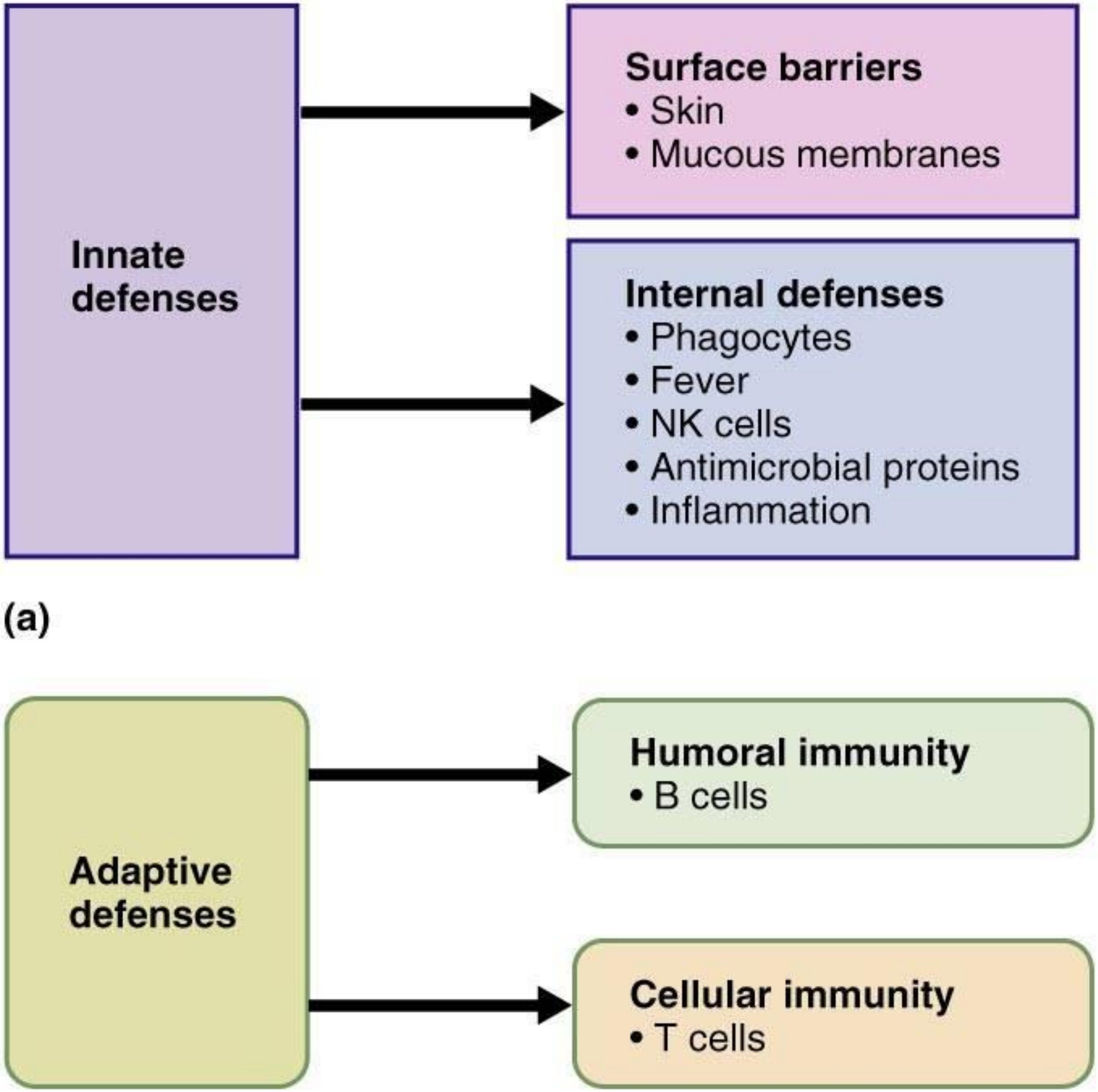
Взаимодействия

- **Клетка – вирус**
- **Клетка-хозяин – Клетка-паразит**

Defense Systems

1. **Innate (nonspecific) defenses**
   - External body membranes
   - Inflammation
     - Antimicrobial proteins, phagocytes and other cells
2. **Adaptive (specific) defenses**
   - T cells and B cells



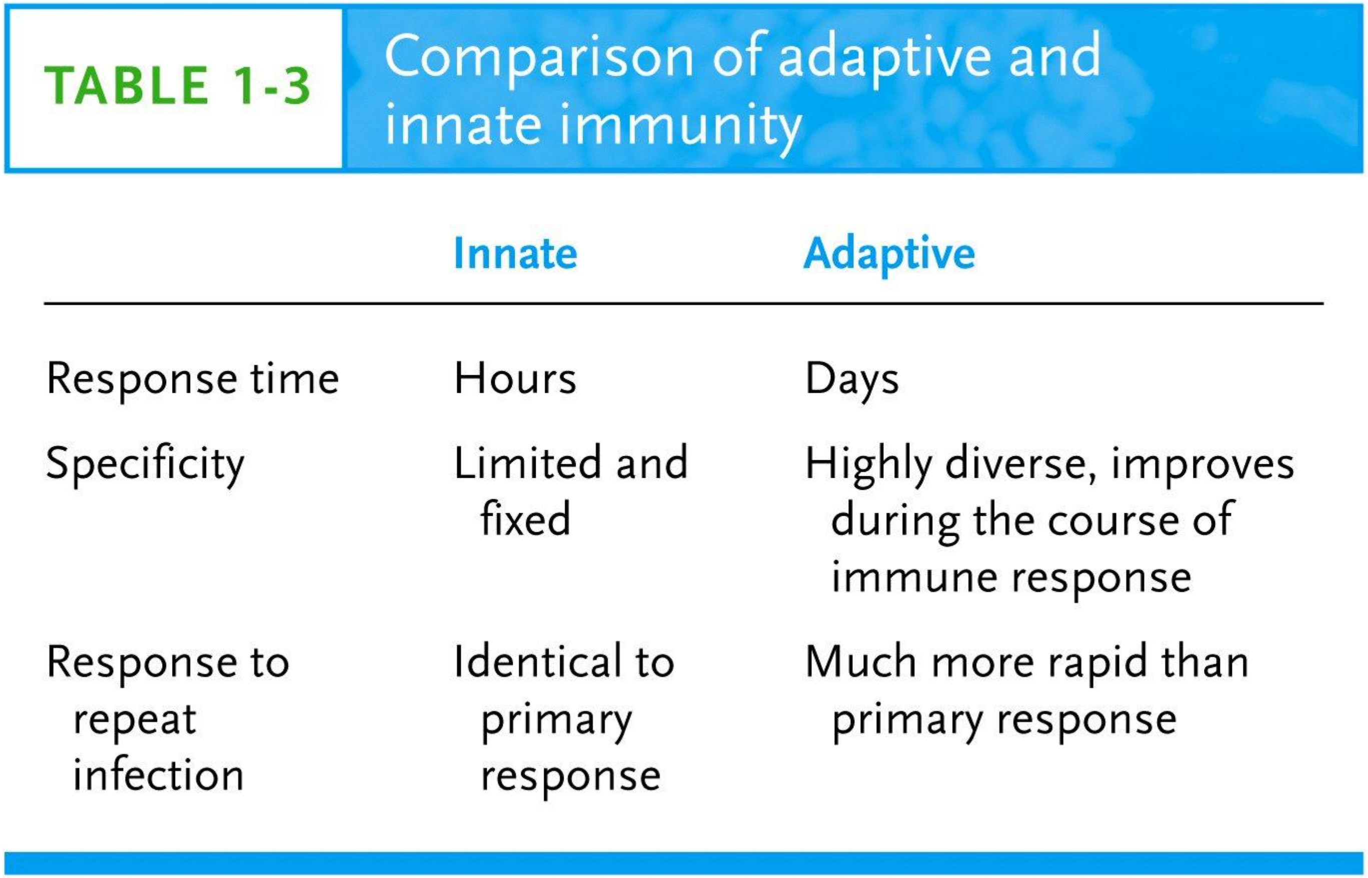
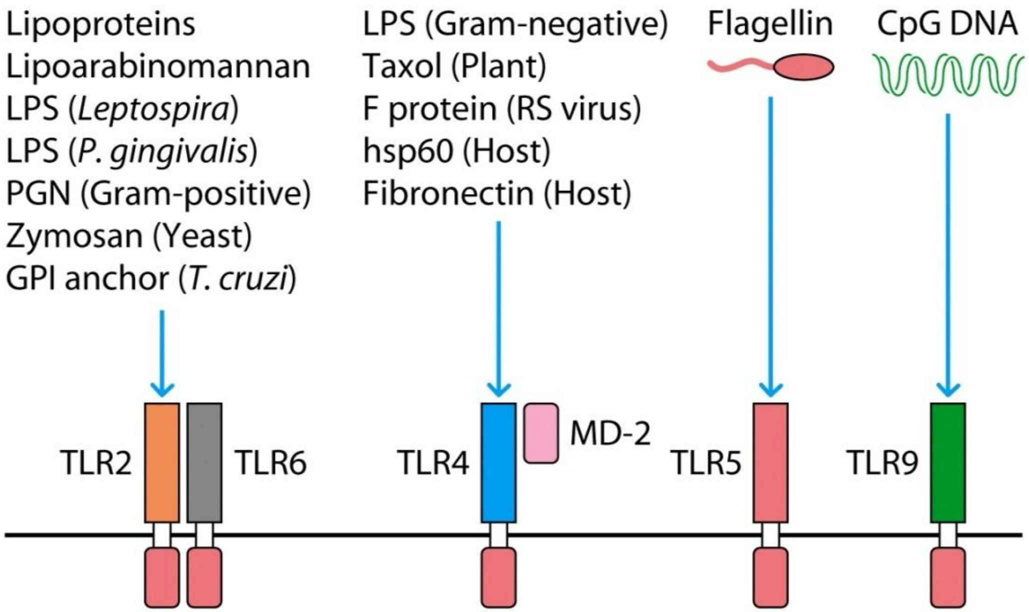


TABLE 1-3 Comparison of adaptive and innate immunity

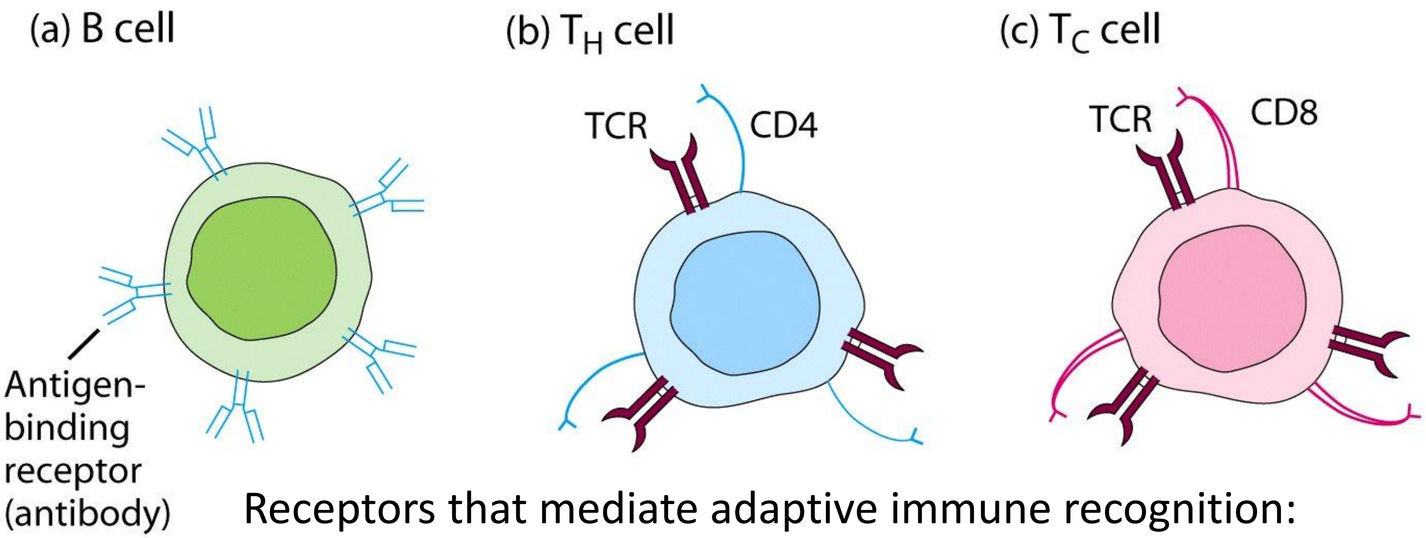
	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse, improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response

Found in:	**all multicellullar organisms**	**Vertebrates only**
Substances that trigger:	**A limited number of pathogen-associated molecular patterns (PAMPs)**	**Virtually any component of pathogens**
Receptors:	**A limited number of Pattern Recognition Receptors (PRRs) expressed on many cells types**	**Highly variable receptors of 2 types: antibody made by B cells and TCR made by T cells**

Comparison of innate and adaptive immune recognition



Receptors that mediate innate immune recognition: Toll-like receptors (TLR)



Receptors that mediate adaptive immune recognition: Antibody and the T cell receptor (TCR)

Innate Defense System: Review

- Surface Barriers
  1. Skin
  2. Mucosal membranes

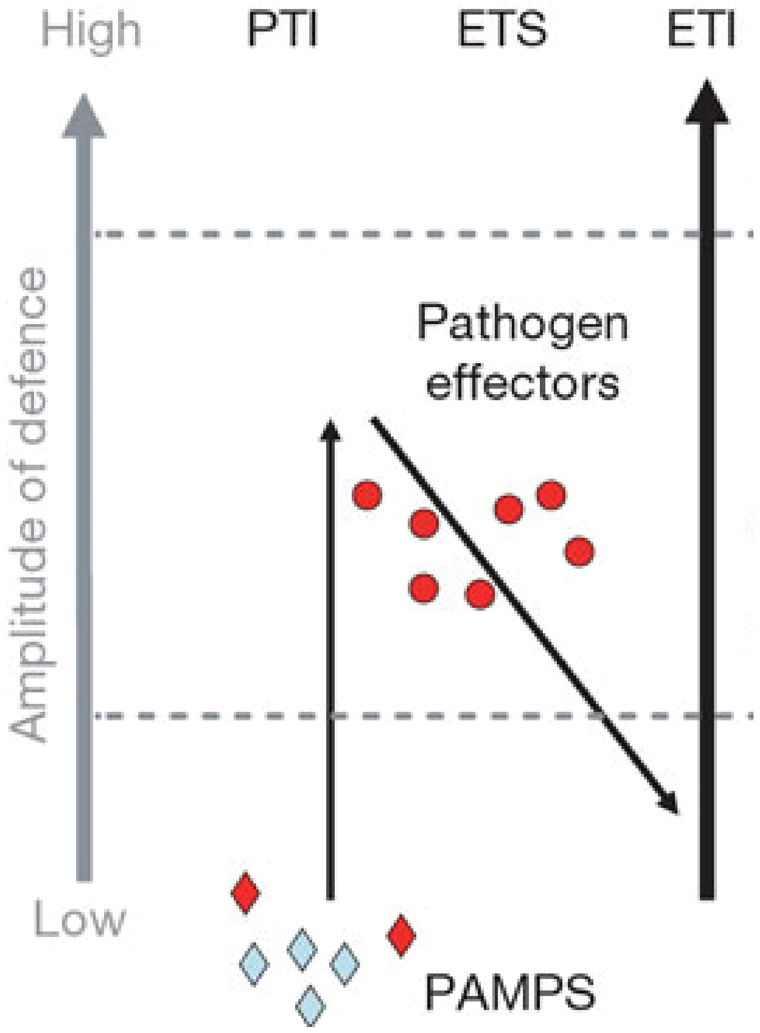
- Internal Nonspecific Defenses
  1. Phagocytes
  2. Natural Killer cells (NK lymphocytes)
  3. Inflammation
  4. Antimicrobial proteins
  5. Fever

TABLE 1-2 Summary of nonspecific host defenses

Type	**Mechanism**
Anatomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3–5) retards growth of microbes.
Mucous membranes	Normal flora compete with microbes for attachment sites and nutrients. Mucus entraps foreign microorganisms. Cilia propel microorganisms out of body.
Physiologic barriers	
Temperature	Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested microorganisms.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis. Toll-like receptors recognize microbial molecules, signal cell to secrete immunostimulatory cytokines. Collectins disrupt cell wall of pathogen.
Phagocytic/endocytic barriers	Various cells internalize (endocytose) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.

Innate Immune Recognition

- All multi-cellular organisms are able to recognize and eliminate pathogens
- Despite their extreme heterogeneity, pathogens share highly conserved molecules, called "**pathogen-associated molecular patterns**" (PAMPs)
- Host cells do not share PAMPs with pathogens
- PAMPs are recognized by innate immune recognition receptors called **pattern-recognition molecules/receptors** (PRMs/PRRs)



Typical PAMPs

- Lipopolysaccharides
- Peptidoglycans
- Certain nucleotide sequences unique to bacteria
- Other bacterial components

Endogenous Signals Induced by PAMPs

- Mediate inflammatory cytokines
- Antigen-presenting cells recognize PAMPs
  - Same APC processes pathogens into specific pathogen-derived antigens and presents them with MHC encoded receptors to T-cells
  - T-cell responds only when presented with both signals
  - Different Effector Cytokines in Response to Different Pathogens (Th1 vs. Th2)

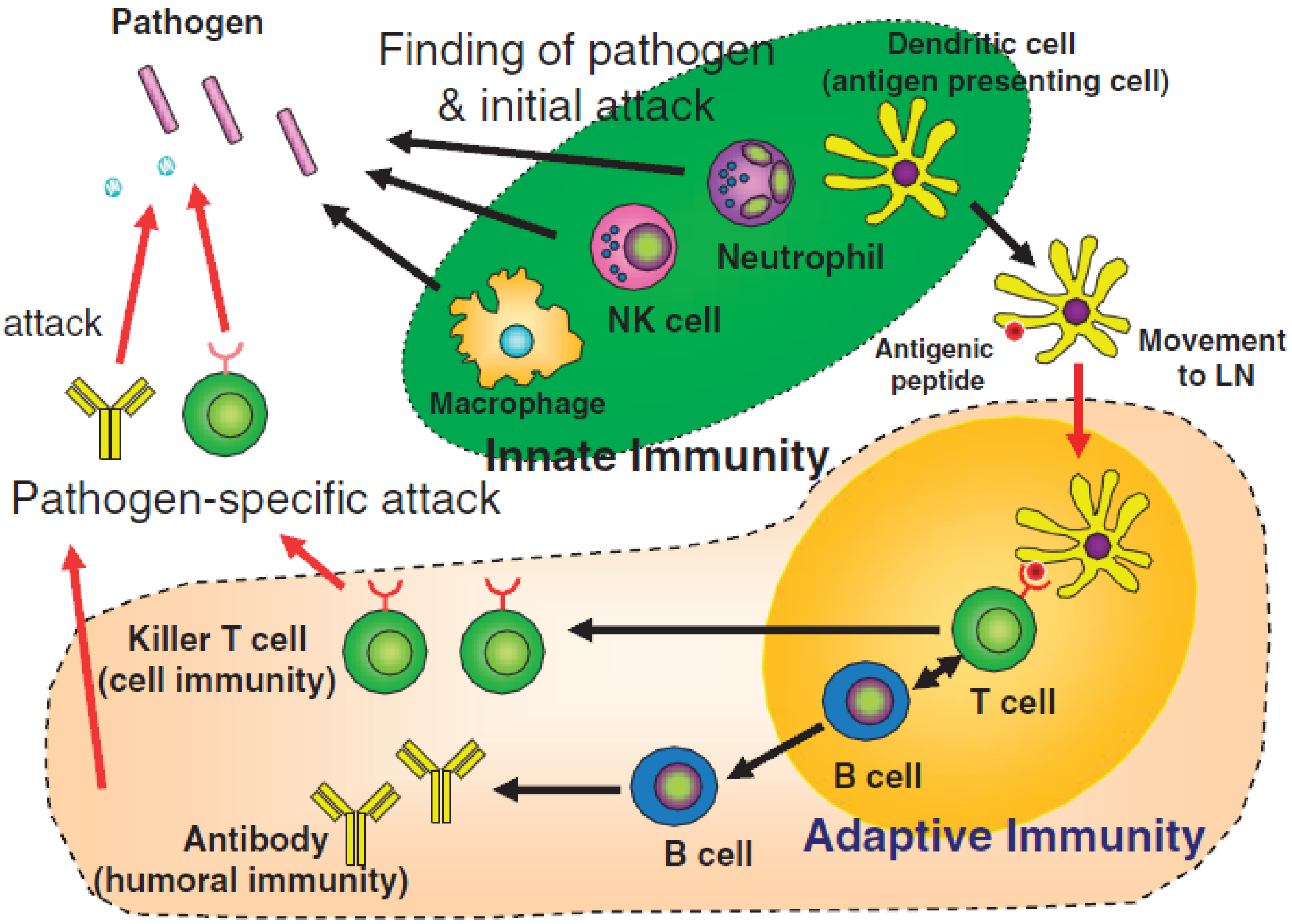
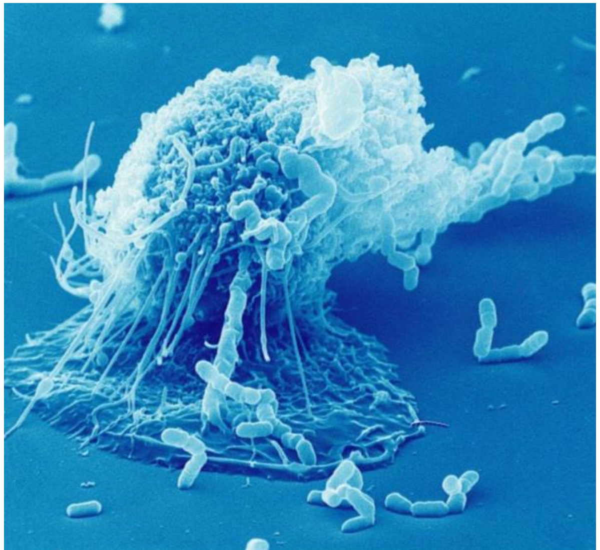
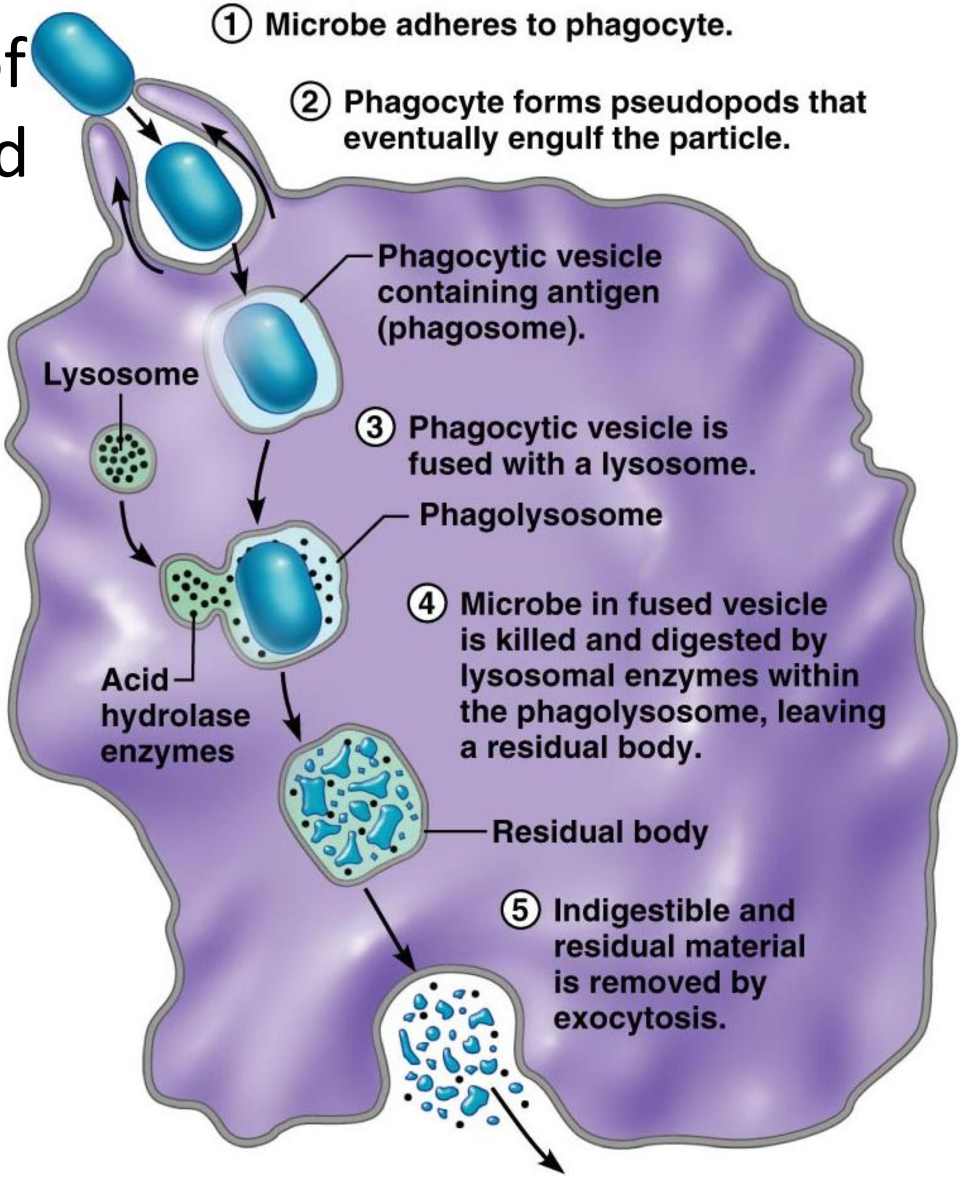


Fig. 2. Innate immunity and adaptive immunity. NK: natural killer; LN: lymphnode.

Mechanism of Phagocytosis

- Chemotaxis
- Adherence – recognition of external carbohydrates and proteins
  - Aided by opsonins
- Ingestion
- Killing and digestion




① Microbe adheres to phagocyte.
② Phagocyte forms pseudopods that eventually engulf the particle.
Phagocytic vesicle containing antigen (phagosome).
Lysosome
③ Phagocytic vesicle is fused with a lysosome.
Phagolysosome
④ Microbe in fused vesicle is killed and digested by lysosomal enzymes within the phagolysosome, leaving a residual body.
Acid hydrolase enzymes
Residual body
⑤ Indigestible and residual material is removed by exocytosis.

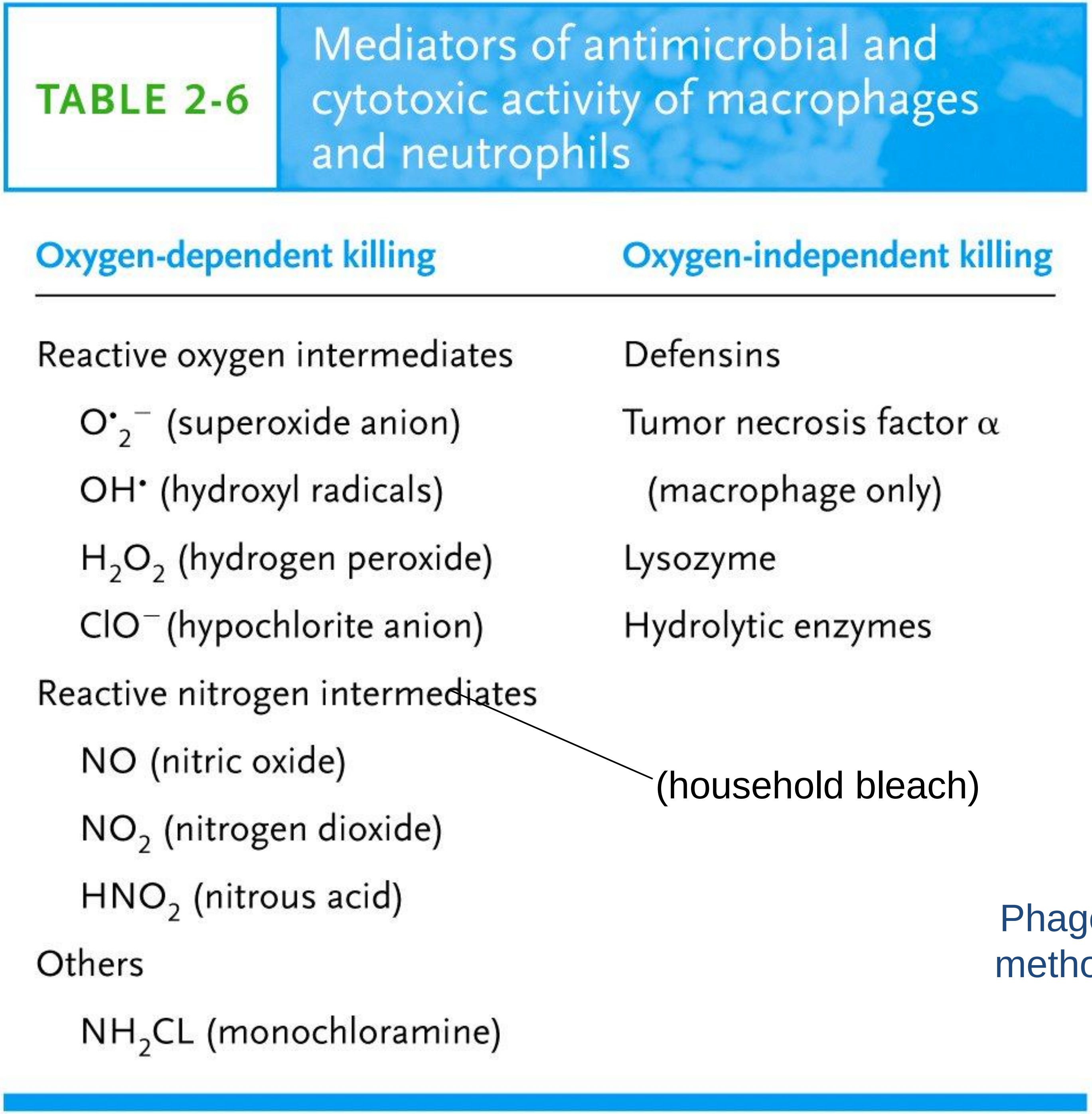


TABLE 2-6 Mediators of antimicrobial and cytotoxic activity of macrophages and neutrophils

Oxygen-dependent killing	Oxygen-independent killing
Reactive oxygen intermediates	Defensins
$O^{\bullet}{}_2^{-}$ (superoxide anion)	Tumor necrosis factor α (macrophage only)
$OH^{\bullet}$ (hydroxyl radicals)	Lysozyme
H_2O_2 (hydrogen peroxide)	Hydrolytic enzymes
ClO^{-} (hypochlorite anion)	
Reactive nitrogen intermediates	
NO (nitric oxide)	
NO_2 (nitrogen dioxide)	
HNO_2 (nitrous acid)	
Others	
NH_2CL (monochloramine)	

(household bleach)

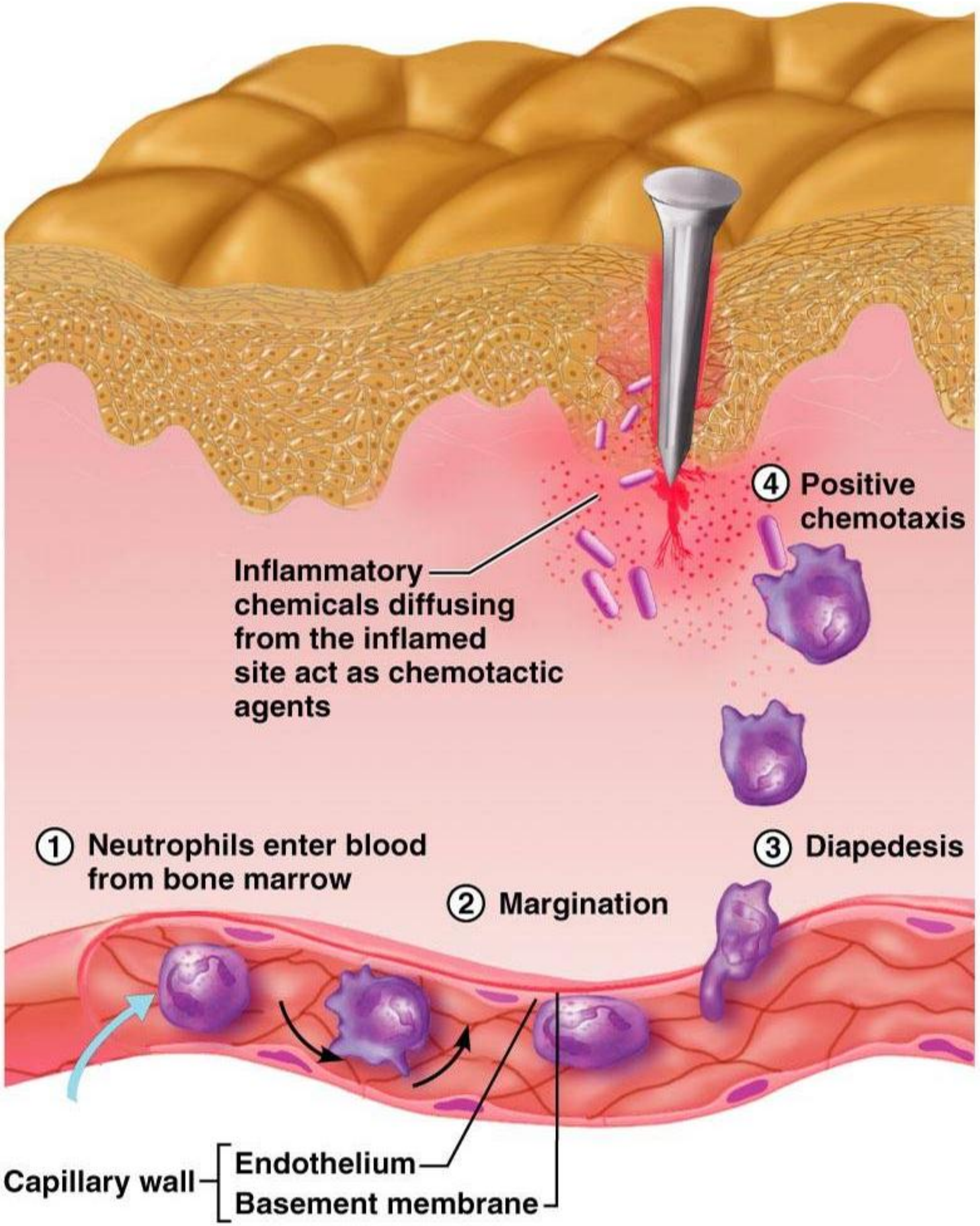
Phagocytes use a variety of methods to destroy ingested microbes.

Innate Defense: Natural Killer Cells

- Distinct group of large granular lymphocytes (NK lymphocytes = Null Killer lymphocytes)
- Nonspecific killers respond to the lack of self-antigens and to the presence of certain surface oligosaccharides
- Kill virus-infected body cells and some tumor **cells by releasing various defensive molecules – not by phagocytosis**
- Act before the antigen-specific immune system is activated
- Secrete potent chemical signals that enhance the inflammatory response

Innate Defense: Inflammation

- Signs:
  1. Redness
  2. Heat
  3. Swelling
  4. Pain
  5. Loss of Function
- Function:
  1. Prevent spread of damage
  2. Dispose of pathogens and debris
  3. Set stage for tissue repair


④ Positive chemotaxis
Inflammatory chemicals diffusing from the inflamed site act as chemotactic agents
① Neutrophils enter blood from bone marrow
③ Diapedesis
② Margination
Capillary wall
Endothelium
Basement membrane

Inflammation causes blood cells to move from blood stream to site of injury

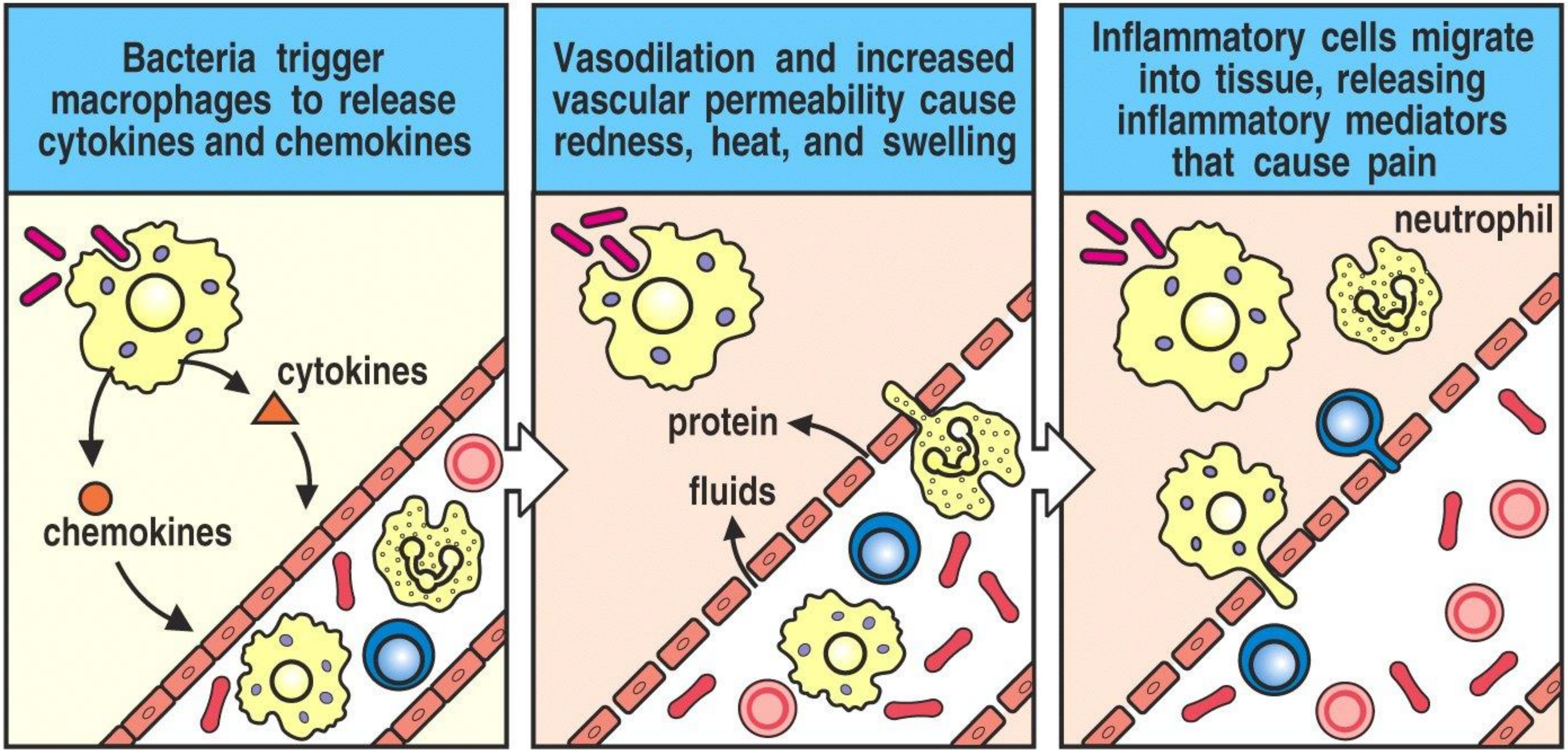

Bacteria trigger macrophages to release cytokines and chemokines
cytokines
chemokines
Vasodilation and increased vascular permeability cause redness, heat, and swelling
protein
fluids
Inflammatory cells migrate into tissue, releasing inflammatory mediators that cause pain
neutrophil

Figure 1-12 Immunobiology, 6/e. (© Garland Science 2005)

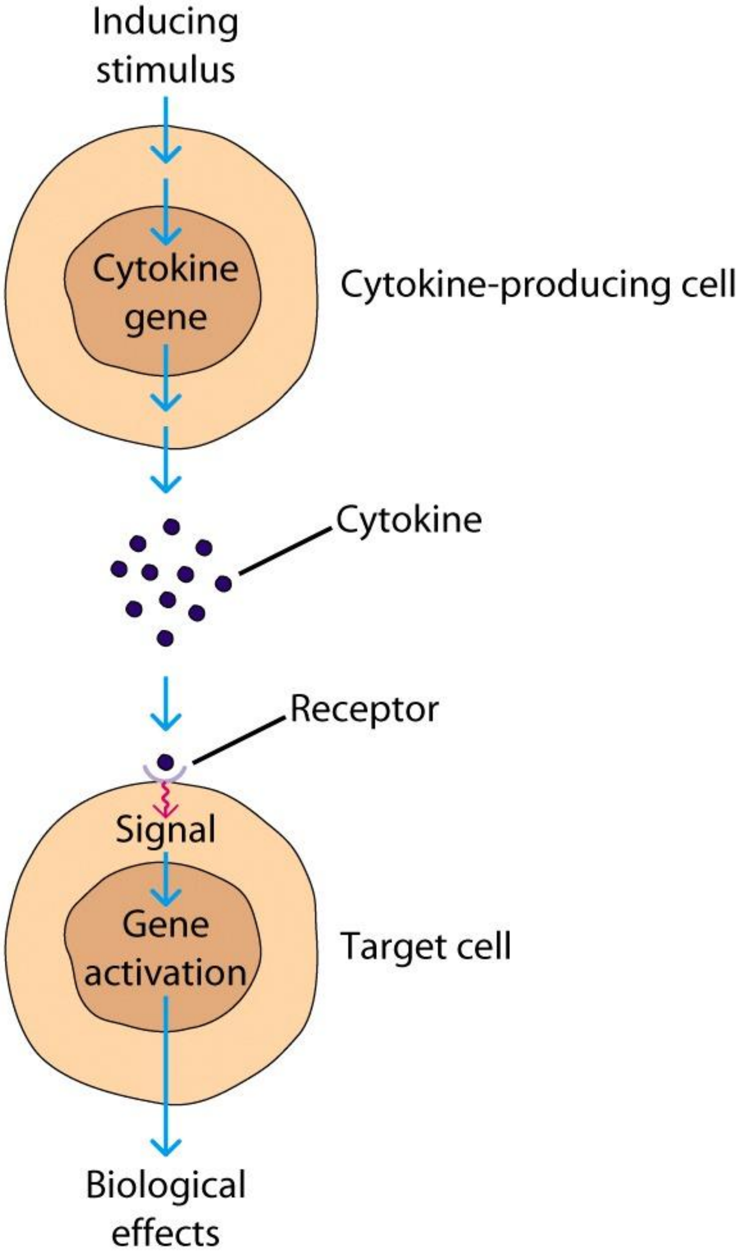
Cytokines: (also called **interleukins**)

Small secreted peptides that used for intracellular communication between cells of the immune system

Can turn on or off immune responses

Mediate inflammation

Chemokines: subset of cytokines that specialize in regulating cell motility



Inflammatory Mediators in Innate Immunity

- Cytokines secreted by phagocytes in response to infection include:
  - IL-1
    - activates vascular endothelium and lymphocytes
    - Increases adhesiveness of leukocytes
  - IL-6
    - Induces B-cell terminal maturation into Ig-producing plasma cells
  - IL-8
    - Induces expression of b2 integrin adhesion molecules on neutrophils, leading to neutrophil migration to infection site
  - IL-12
    - Activates NK cells and induces Th1-cell differentiation
  - IL-18
  - TNF-α
    - Activates vascular endothelium and increases vascular permeability, leading to accumulation of Ig and complement in infected tissues

Other Mediators and Molecules

- Phagocytes
  - Toxic oxygen radicals
  - Peroxides
  - Nitric oxide (NO)
  - Lipid mediators of inflammation
    - Prostaglandins
    - LTB4
    - Platelet activating factor
- Complement component C5a
  - Stimulates mast cells to release histamine, serotonin and LTB4
- IL-1, IL-6 and TNF-α
  - Induce acute-phase response in liver
  - Induce fever
- IL-1 and IL-18 signaling pathways activate NF-κB, important in innate immunity

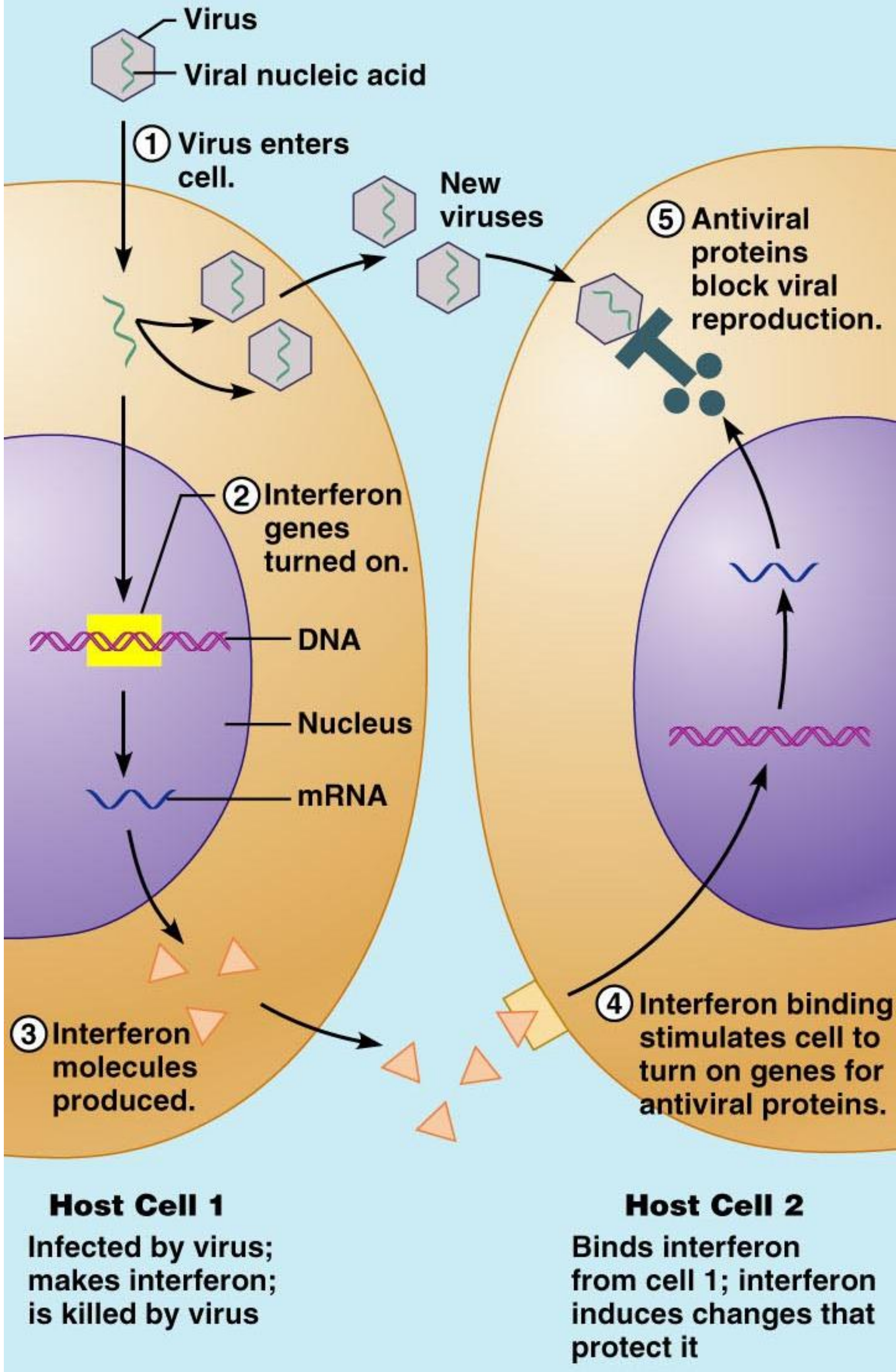
Innate Defense: Antimicrobial Proteins

1. Attack microorganisms directly
2. Interfere with microbial reproduction

- The most important are:
    1. Interferons
    2. The Complement System
    3. Transferrins which bind Fe^{2+} in plasma, inhibiting bacterial growth

Interferons (IFNs)

- Produced by most tissue cells when infected by a virus
- Diffuses to uninfected cells and binds to surface receptors
  - stimulates macrophages and natural killer lymphocytes
  - stimulates production of **antiviral proteins** which block viral replication
  - inhibits growth of virally infected cells
  - suppresses growth of tumor cells
- ***Alpha IFN*** is used against:
  - hepatitis C virus
  - herpes virus (genital warts)


Virus
Viral nucleic acid
① Virus enters cell.
New viruses
⑤ Antiviral proteins block viral reproduction.
② Interferon genes turned on.
DNA
Nucleus
mRNA
③ Interferon molecules produced.
④ Interferon binding stimulates cell to turn on genes for antiviral proteins.
Host Cell 1
Infected by virus; makes interferon; is killed by virus
Host Cell 2
Binds interferon from cell 1; interferon induces changes that protect it

Antimicrobial Peptides/Defensins

- Four hundred peptides described to date
- Defensins (3- 5-kD, four families in eukaryotes)
  - α-defensins (neutrophils and intestinal Paneth cells)
  - β-defensins (epithelial cells)
  - Insect defensins
  - Plant defensins
- Defensins appear to act by binding to outer membrane of bacteria, resulting in increased membrane permeability.
- May also play a role in inflammation and wound repair

Complement System

- Three pathways now known
  - Classical
  - Alternative
  - Lectin or MBL pathway (binding to mannose-containing carbohydrates)
- Host cells have complement regulatory proteins on their surface that protect them from spontaneous activation of C3 molecules

The Complement System

- 20 plasma and cell membrane proteins that exist as inactive precursors
- When activated, the complement system functions to “complement” or enhance certain immune, inflammatory, and allergic responses
- Kills bacteria and certain other microbial cell types (our cells normally are protected from complement attack)
- Stimulates chemotaxis in leuckocytes
- Enhances the effectiveness of both nonspecific and specific defenses

Complement Pathways

Classical Pathway is triggered by the specific immune system

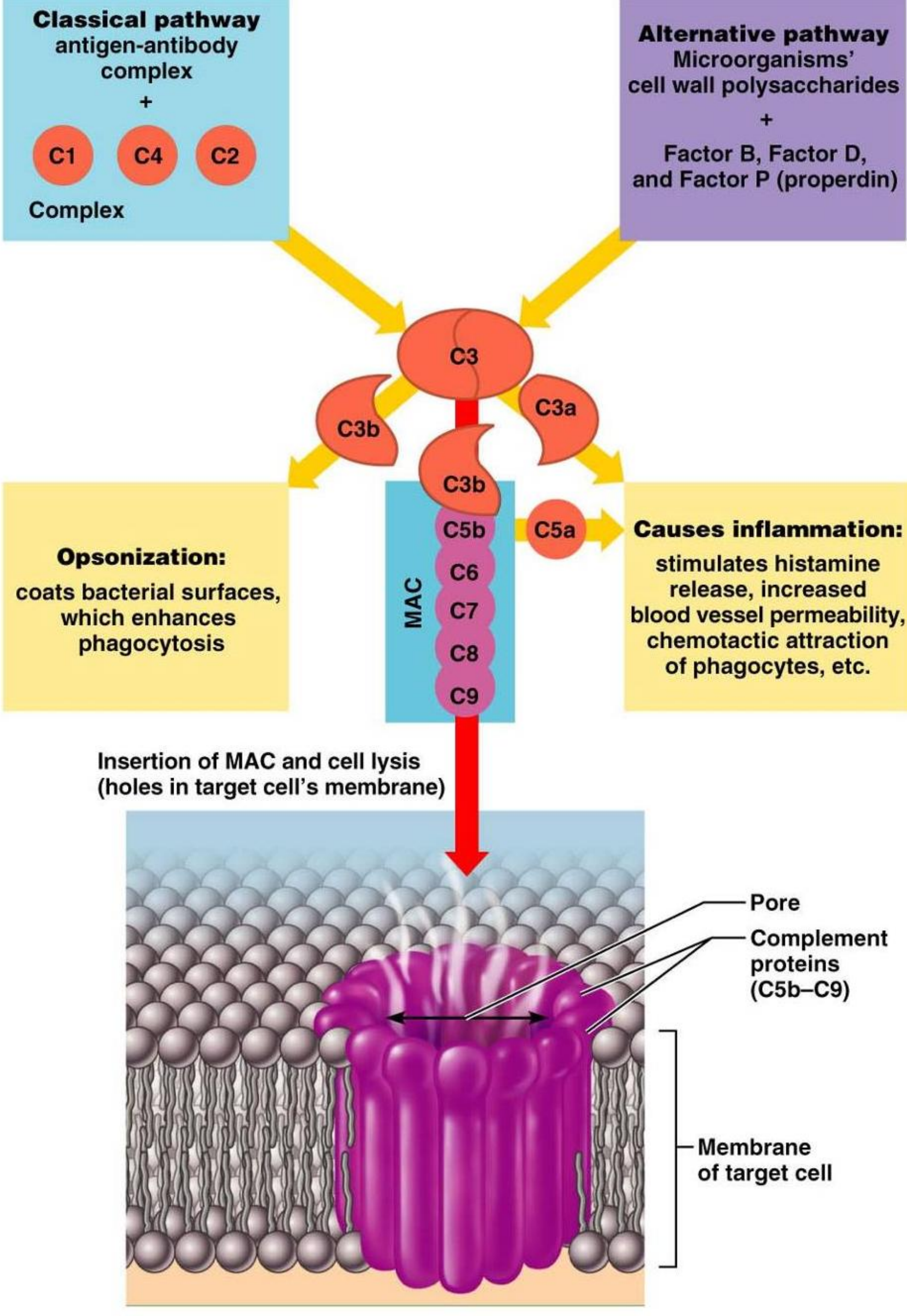
- Requires binding of antibodies to antigens of invading organisms
- Complement C1 then binds to the antigen-antibody complexes (complement fixation)

Alternative Pathway is triggered by non-specific interaction among factors B, D, and P, and microbial cell wall polysaccharides (complement fixation)

Both pathways involve an enzyme cascade

Complement Pathways

- Both pathways converge on C3, which cleaves into C3a and C3b
- C3b initiates formation of a **membrane attack complex (MAC)**
- MAC causes cell lysis by creating many hundreds of microscopic holes in the cell's plasmalemma
- C3b is also an opsonin


Classical pathway
antigen-antibody complex
+
C1
C4
C2
Complex
Alternative pathway
Microorganisms' cell wall polysaccharides
+
Factor B, Factor D, and Factor P (properdin)
C3
C3b
C3a
C3b
C5b
C6
C7
C8
C9
MAC
C5a
Opsonization:
coats bacterial surfaces, which enhances phagocytosis
Causes inflammation:
stimulates histamine release, increased blood vessel permeability, chemotactic attraction of phagocytes, etc.
Insertion of MAC and cell lysis (holes in target cell's membrane)
Pore
Complement proteins (C5b–C9)
Membrane of target cell

Innate Defense: Fever

- **Pyrogens** reset the temperature set-point in the hypothalamus
- Inhibits some microbes from growing
- Increases body's metabolic rate, which speeds up immune defenses and tissue repair
- Increases effects of antimicrobial substances produced by the immune system
- Stimulates liver and spleen to sequester iron and zinc (needed by microorganisms)
- *High fevers are dangerous*

Innate Defense System: Review

- Surface Barriers
  1. Skin
  2. Mucosal membranes

- Internal Nonspecific Defenses
  1. Phagocytes
  2. Natural Killer cells (NK lymphocytes)
  3. Inflammation
  4. Antimicrobial proteins
  5. Fever

Summary of Innate Immunity

- External and mechanical barriers
- Receptors for pathogen motifs
- Soluble antimicrobial proteins
- Pattern of cytokines produced influences adaptive response

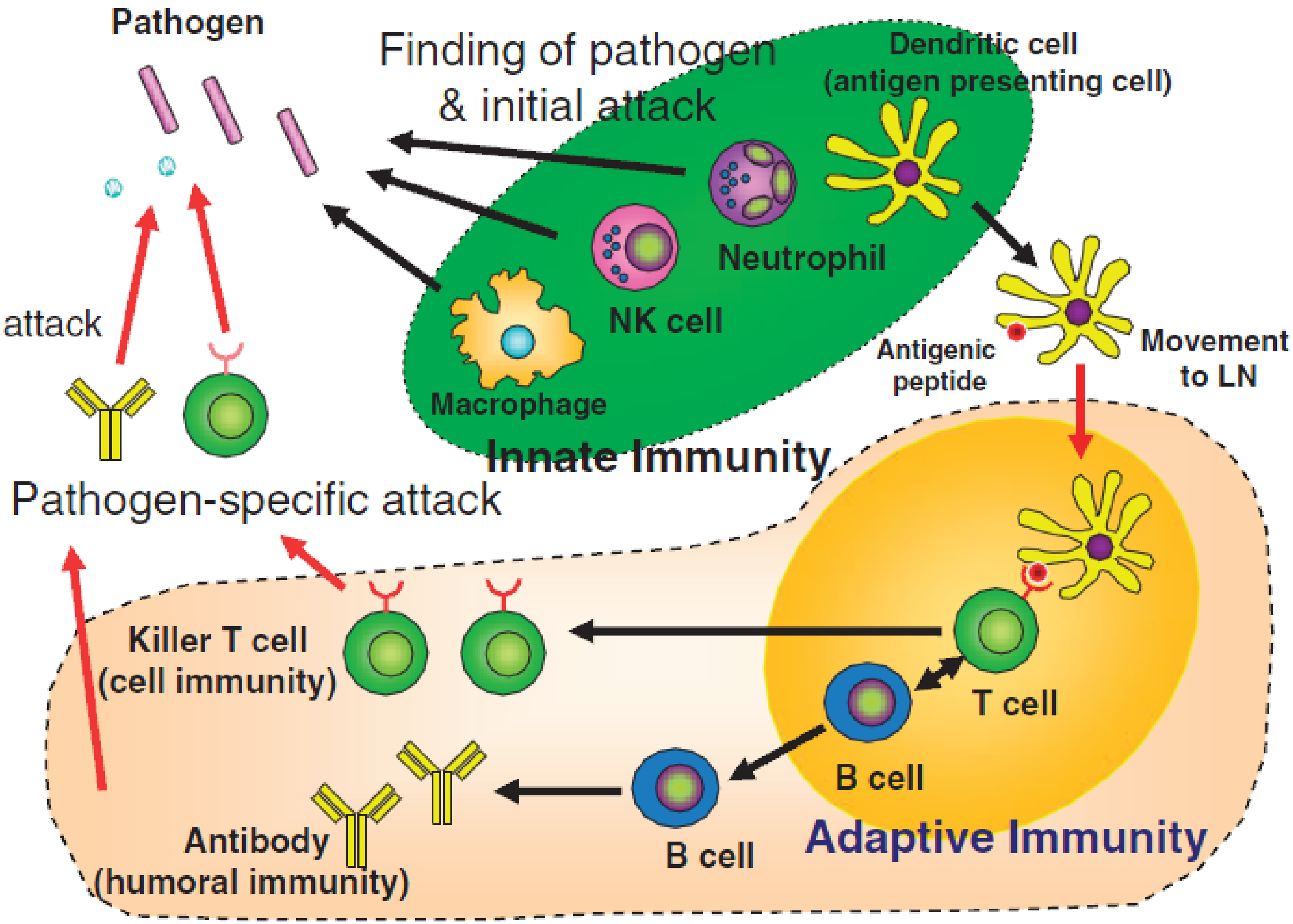


Fig. 2. Innate immunity and adaptive immunity. NK: natural killer; LN: lymphnode.

Adaptive Defense

- The adaptive immune system:
  - Acts to immobilize, neutralize, or destroy foreign substances and cells
  - Amplifies the inflammatory response and activates complement
  - Is antigen-specific*, systemic, and has memory
    - *Recognizes specific foreign molecules
  - Has two interdependent arms
    - Humoral, or antibody-mediated immunity (AMI)
    - Cellular, or cell-mediated immunity (CMI)

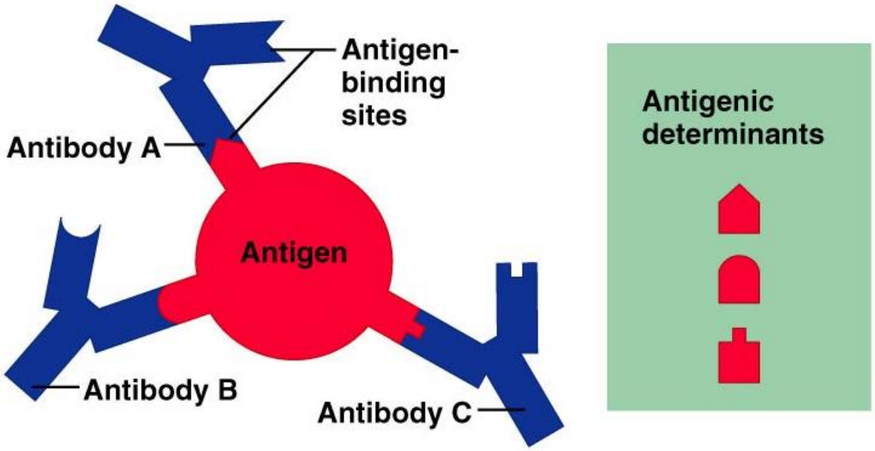
Adaptive Defense

- Definitions:
  - Immunity: the ability of the body to defend itself against specific foreign invaders (molecules or cells)
  - Immunogenicity: the ability to stimulate proliferation of specific lymphocytes and specific antibody production
  - Reactivity: the ability of activated lymphocytes and their products, antibodies, etc., to interact with specific antigens

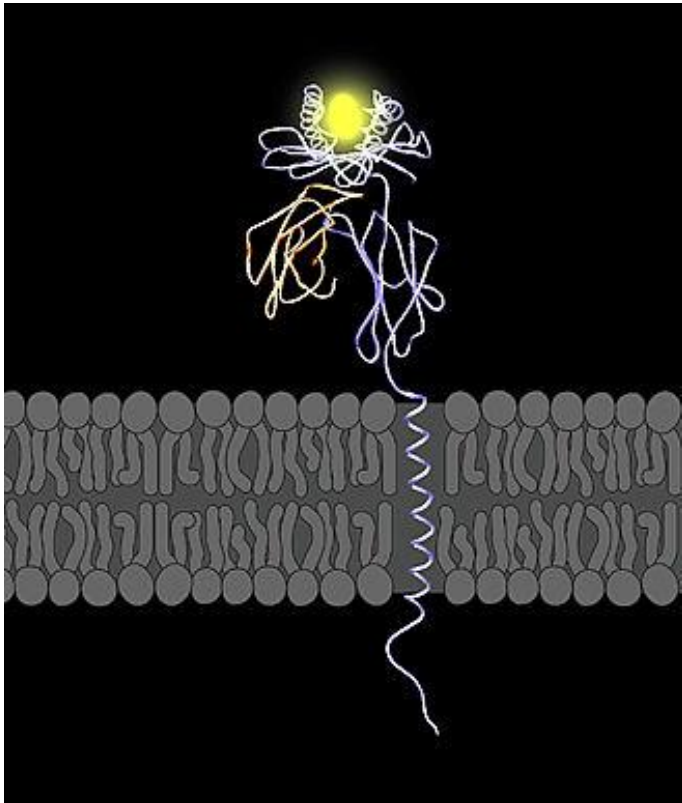
Adaptive Defense

- Definitions:
  - Specificity: the antigen triggers focused immune defenses (from particular lymphocytes lineages) that respond only to the antigens of this foreign substance/cell
  - Memory: the immune system produces clones of specific memory lymphocytes (T & B) which react rapidly when the particular foreign substance/cell is encountered again
  - *Specificity* and *memory* differentiate this system from the nonspecific (innate) defenses

Adaptive Defense



- Antigen receptor diversity
  - >1 billion different antigenic determinants are recognized by the body
  - Genetic recombination shuffles and reorganizes different Ab genes
- Major histocompatibility complex antigens (MHC)
  - unique to each individual’s cells; help in identifying what is self versus foreign
  - 2 classes of MHC antigens (“markers”)
    - class I MHC – found on all body cells except RBC's
    - class II MHC - only on antigen presenting cells (APC’s), thymus cells, and activated T cells



Antigen-Presenting Cells (APCs)

- APCs phagocytize, process, and present antigens to lymphocytes
- APCs do not respond to specific antigens
- APCs contribute to coordinating specific immunity
  - Macrophages
  - Dendritic (Langerhans) cells
  - B lymphocytes

The major initiators of adaptive immunity are APCs, which actively migrate to the lymph nodes and secondary lymphoid organs and present antigens to T and B cells

Class I MHC Proteins

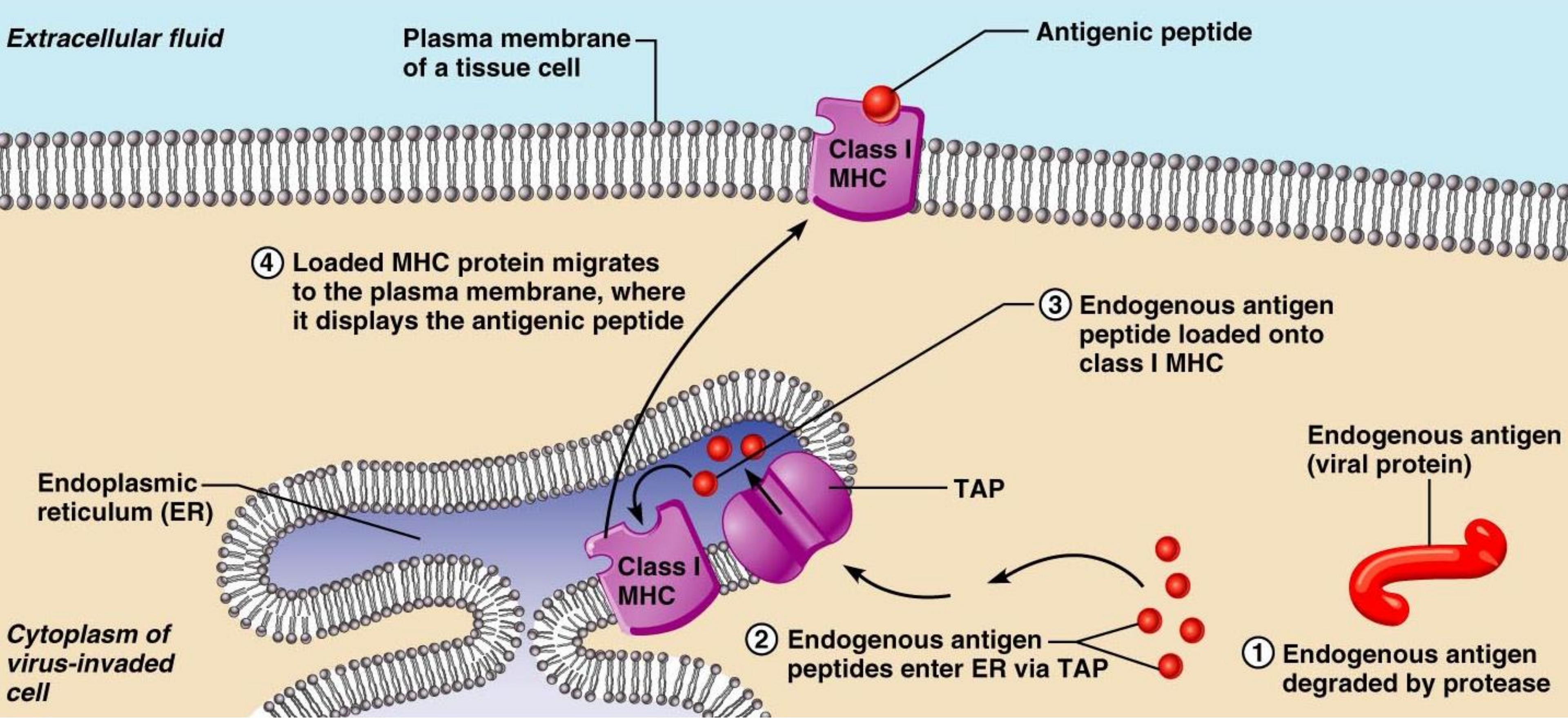
- Found on all cells, except RBCs

- Recognized by T lymphocytes and APCs

- Display peptides from endogenous antigens
  - Endogenous antigens are:
    - Associated with body cells
    - Degraded by proteases and enter the endoplasmic reticulum
    - Transported through special membrane channels
    - Bound with MHC class I molecules on the ER membrane
    - Migrate to the cell membrane as a complex: Ag -- MHC class I molecule

MHC Class I Proteins

This is a form of Antigen Presentation


Extracellular fluid
Plasma membrane of a tissue cell
Antigenic peptide
Class I MHC
④ Loaded MHC protein migrates to the plasma membrane, where it displays the antigenic peptide
③ Endogenous antigen peptide loaded onto class I MHC
Endogenous antigen (viral protein)
Endoplasmic reticulum (ER)
TAP
Class I MHC
Cytoplasm of virus-invaded cell
② Endogenous antigen peptides enter ER via TAP
① Endogenous antigen degraded by protease

Cancer cells often do something quite similar to the virus-infected cells.
(Foreign MHC Class I Ags are the source of tissue transplant rejections.)

MHC Class II Proteins

1. Immune cell identity markers found only on mature B cells, some T cell classes, and antigen-presenting cells

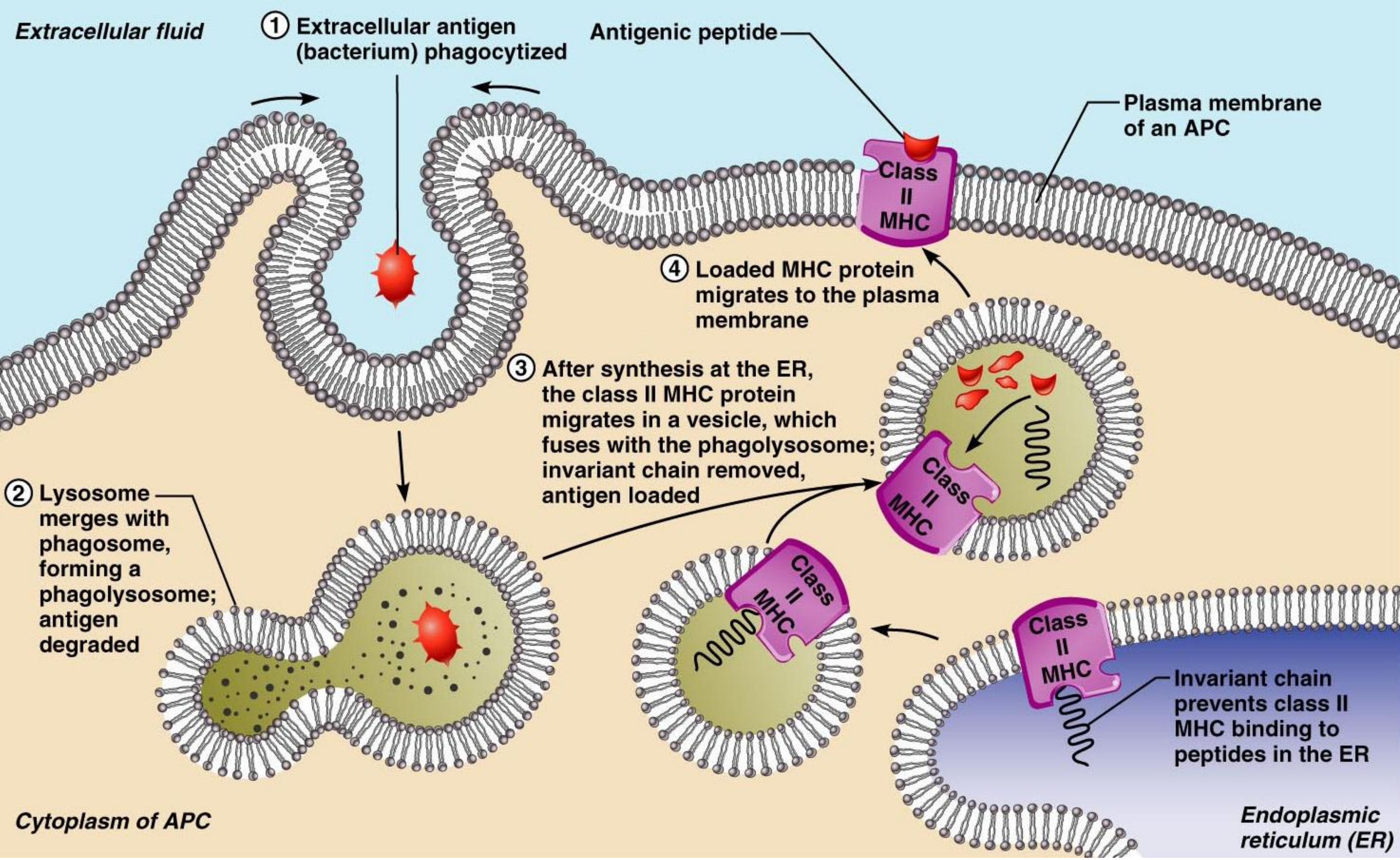
2. MHC Class II proteins are synthesized in the ER

3. A phagosome containing a pathogen (with exogenous antigens) merges with a lysosome

4. MHC Class II proteins migrate into the phagosome where the antigen macromolecules are degraded and particular antigen peptides are bound to the MHC Class II markers

5. *Ag-- MHC class II complex* then migrates to the cell membrane and displays antigenic peptide for recognition by CD4 T_H cells

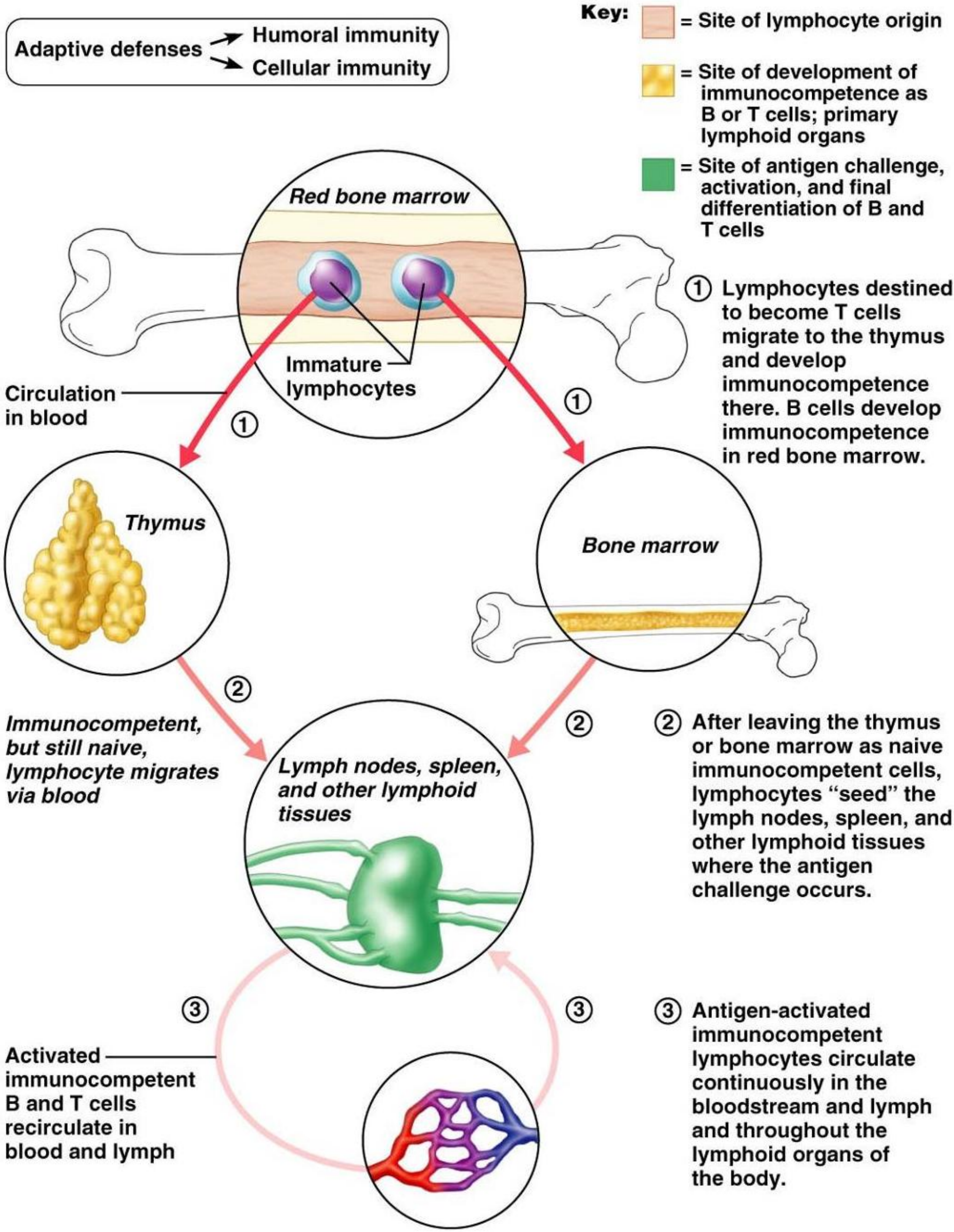
MHC Class II Proteins


Extracellular fluid
① Extracellular antigen (bacterium) phagocytized
Antigenic peptide
Plasma membrane of an APC
Class II MHC
④ Loaded MHC protein migrates to the plasma membrane
③ After synthesis at the ER, the class II MHC protein migrates in a vesicle, which fuses with the phagolysosome; invariant chain removed, antigen loaded
② Lysosome merges with phagosome, forming a phagolysosome; antigen degraded
Class II MHC
Class II MHC
Class II MHC
Invariant chain prevents class II MHC binding to peptides in the ER
Cytoplasm of APC
Endoplasmic reticulum (ER)

This is a key function of our APCs in most Ag-specific defenses.

Lymphocytes Provide Ag Specificity

- B and T lymphocytes develop in bone marrow
- Lymphocytes mature and develop immunocompetence (ability to recognize specific antigen) in different locations
  - **B** cells mature in the **b**one marrow and provide *Ab-mediated* immunity
  - **T** cells mature in the **t**hymus and provide *cell-mediated* immunity


Adaptive defenses
Humoral immunity
Cellular immunity
Red bone marrow
Immature lymphocytes
Circulation in blood
①
①
Thymus
Bone marrow
②
②
Immunocompetent, but still naive, lymphocyte migrates via blood
Lymph nodes, spleen, and other lymphoid tissues
③
③
Activated immunocompetent B and T cells recirculate in blood and lymph

Key:
🟫 = Site of lymphocyte origin
🟨 = Site of development of immunocompetence as B or T cells; primary lymphoid organs
🟩 = Site of antigen challenge, activation, and final differentiation of B and T cells

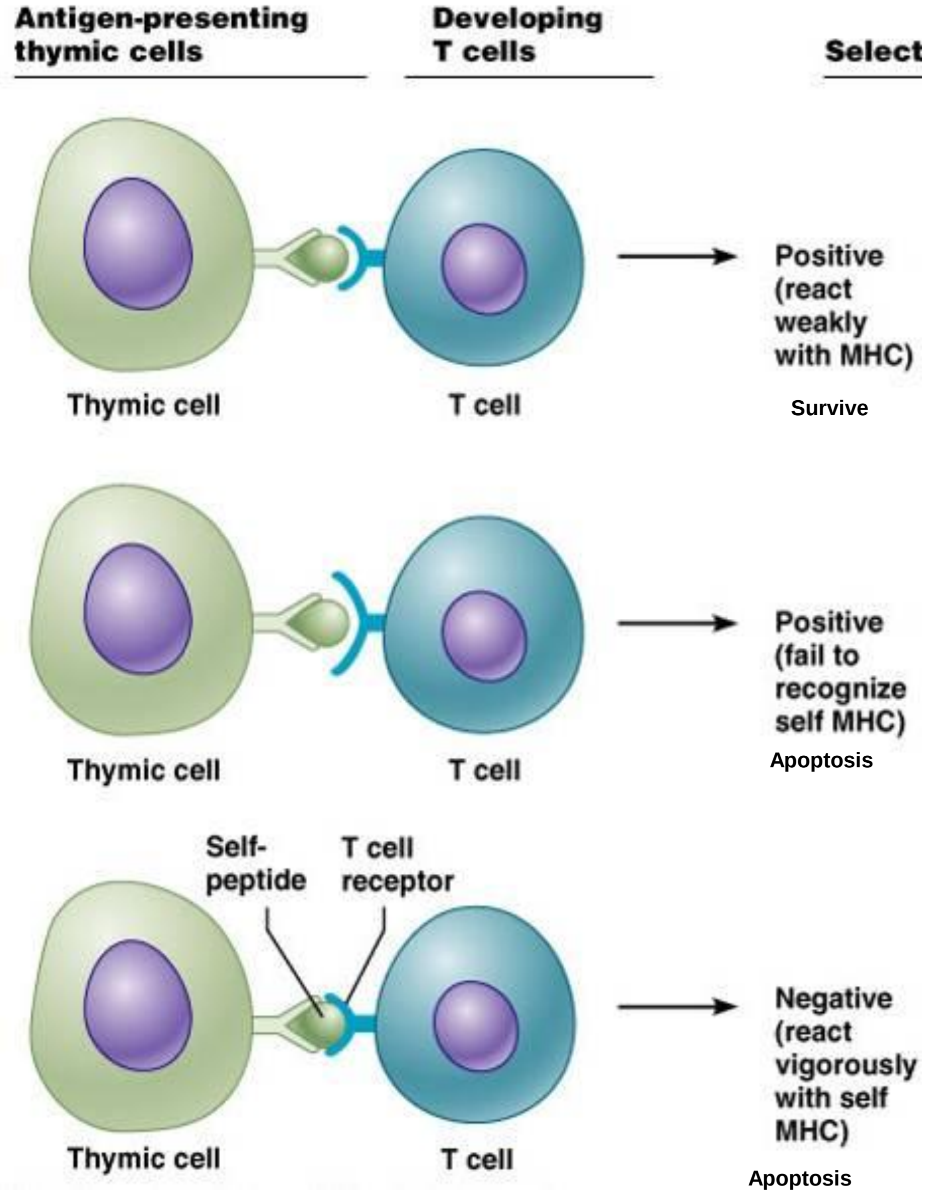
① Lymphocytes destined to become T cells migrate to the thymus and develop immunocompetence there. B cells develop immunocompetence in red bone marrow.

② After leaving the thymus or bone marrow as naive immunocompetent cells, lymphocytes "seed" the lymph nodes, spleen, and other lymphoid tissues where the antigen challenge occurs.

③ Antigen-activated immunocompetent lymphocytes circulate continuously in the bloodstream and lymph and throughout the lymphoid organs of the body.

Immunocompetent T Cells

- T cells mature in the thymus under positive and negative selection pressures
  - Positive selection – outer thymic cortex
    - Selects functional T cells which become both immunocompetent and potentially self-tolerant
    - Non-selected cells die via apoptosis
  - Negative selection – inner thymic cortex
    - Kill or regulate off T cells that react with self-antigens


Antigen-presenting thymic cells
Developing T cells
Select
Thymic cell
T cell
Positive (react weakly with MHC)
Survive
Thymic cell
T cell
Positive (fail to recognize self MHC)
Apoptosis
Self-peptide
T cell receptor
Thymic cell
T cell
Negative (react vigorously with self MHC)
Apoptosis

Immunocompetent B Cells

- B cells become immunocompetent and self-tolerant in **b**one marrow
  - Some self-reactive B cells are killed by apoptosis (clonal deletion)
  - Some self-reactive B cells can modify their anti-self properties (receptor editing)
- Some self-reactive B cells are released from the bone and are inactivated by negative regulation (*anergy*)

Cell-Mediated Immunity

- CMI is involved in most aspects of specific immune defense

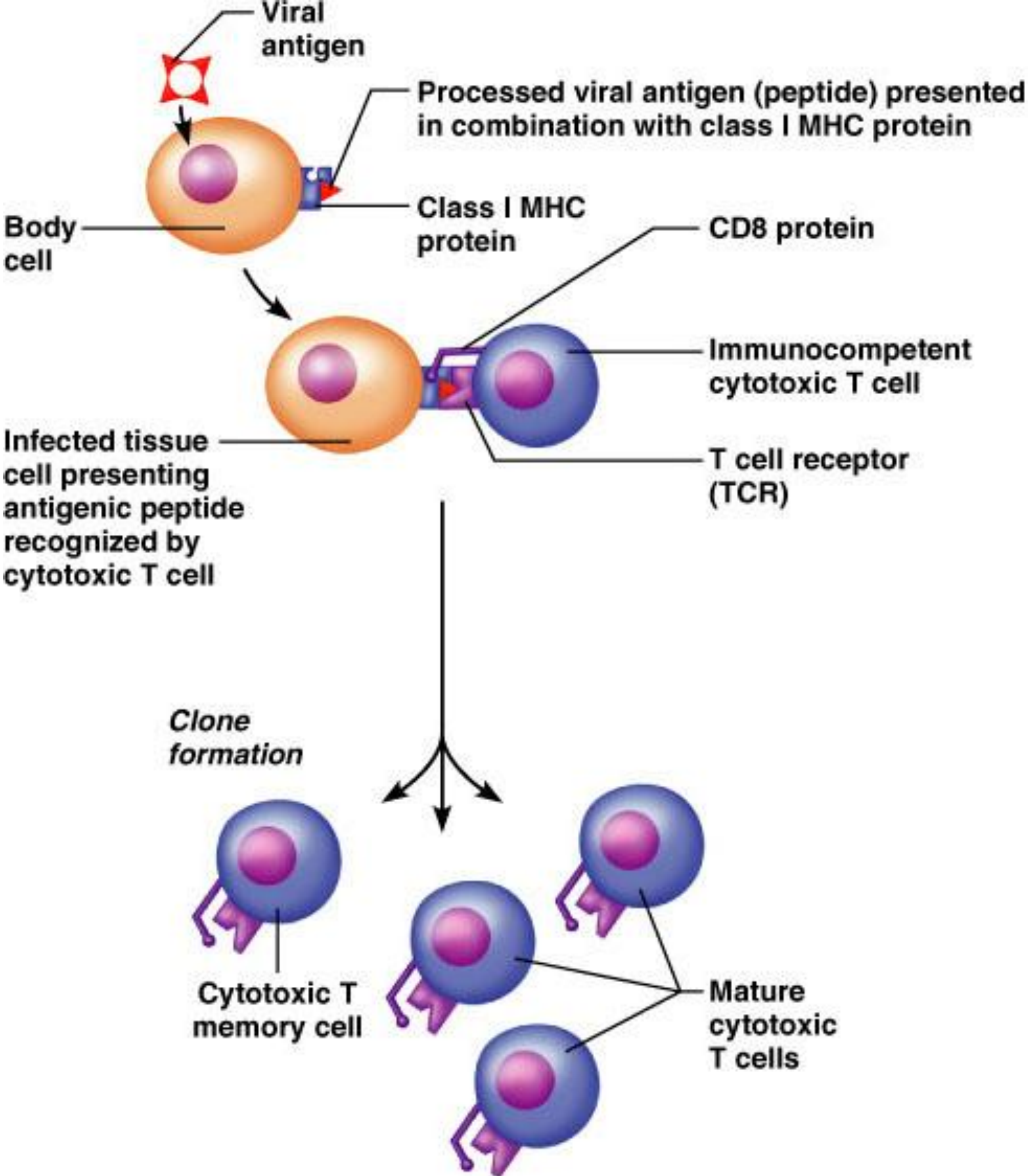
- Three populations of T lymphocytes regulate specific immunity

  - Helper T_H cells which carry CD4+ markers
  - Suppressor T_S cells
  - Memory T cells

- cytotoxic T_C cells which carry CD8+ markers destroy tumor cells and virus-infected cells; they also attack transplanted cells and tissues

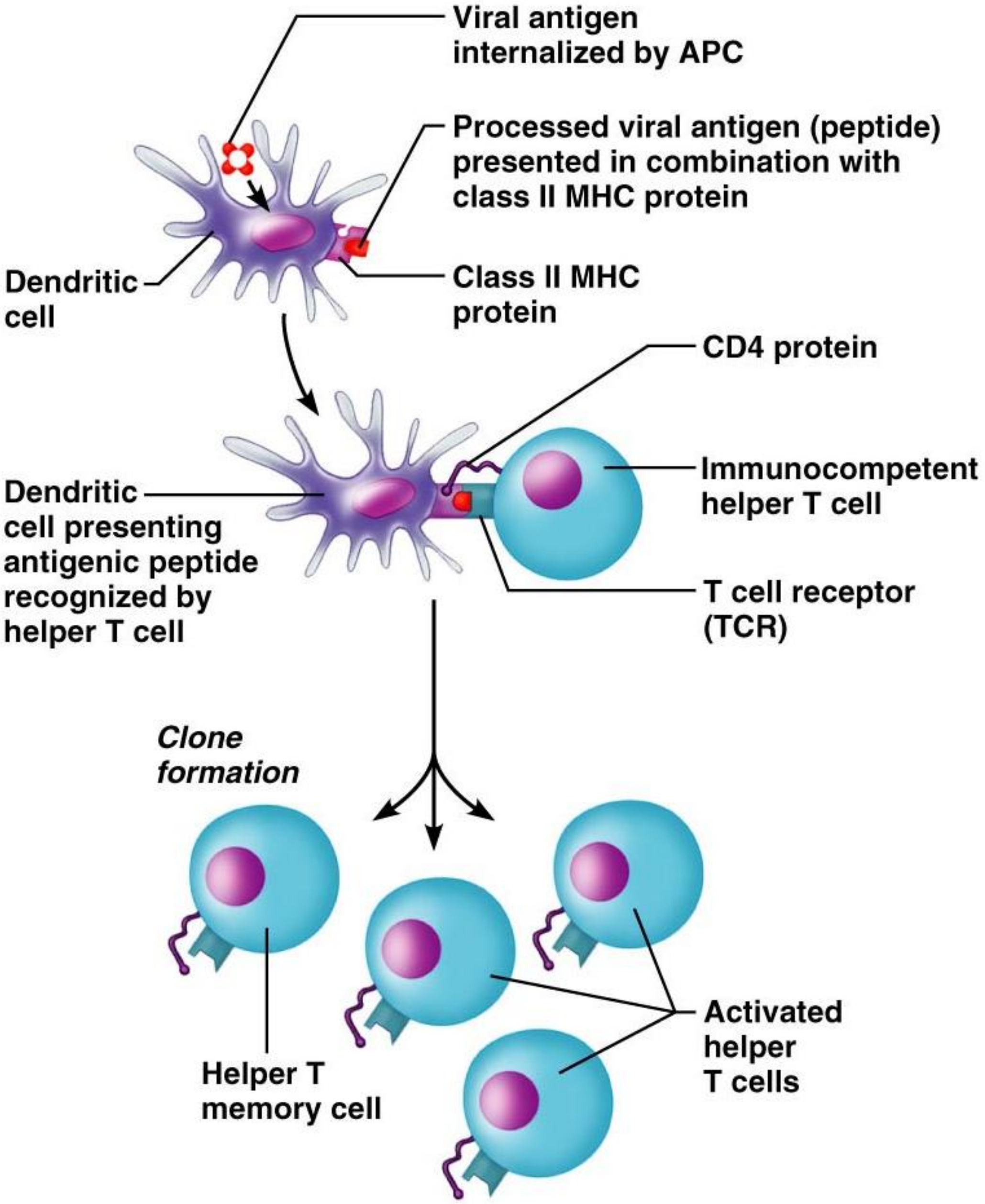
T Cell Activation- Step 1:

Antigen Binding and Antigen Presentation


Viral antigen
Processed viral antigen (peptide) presented in combination with class I MHC protein
Class I MHC protein
Body cell
CD8 protein
Immunocompetent cytotoxic T cell
Infected tissue cell presenting antigenic peptide recognized by cytotoxic T cell
T cell receptor (TCR)
Clone formation
Cytotoxic T memory cell
Mature cytotoxic T cells

T Cell Activation- Step 2: Co-Stimulation

- T cells must bind to MHC Class II surface receptors on an APC
- After co-stimulation with cytokines, T cells enlarge, proliferate, and form clones
- Activated T cells differentiate and perform functions according to their T cell class


Viral antigen internalized by APC
Processed viral antigen (peptide) presented in combination with class II MHC protein
Dendritic cell
Class II MHC protein
CD4 protein
Dendritic cell presenting antigenic peptide recognized by helper T cell
Immunocompetent helper T cell
T cell receptor (TCR)
Clone formation
Helper T memory cell
Activated helper T cells

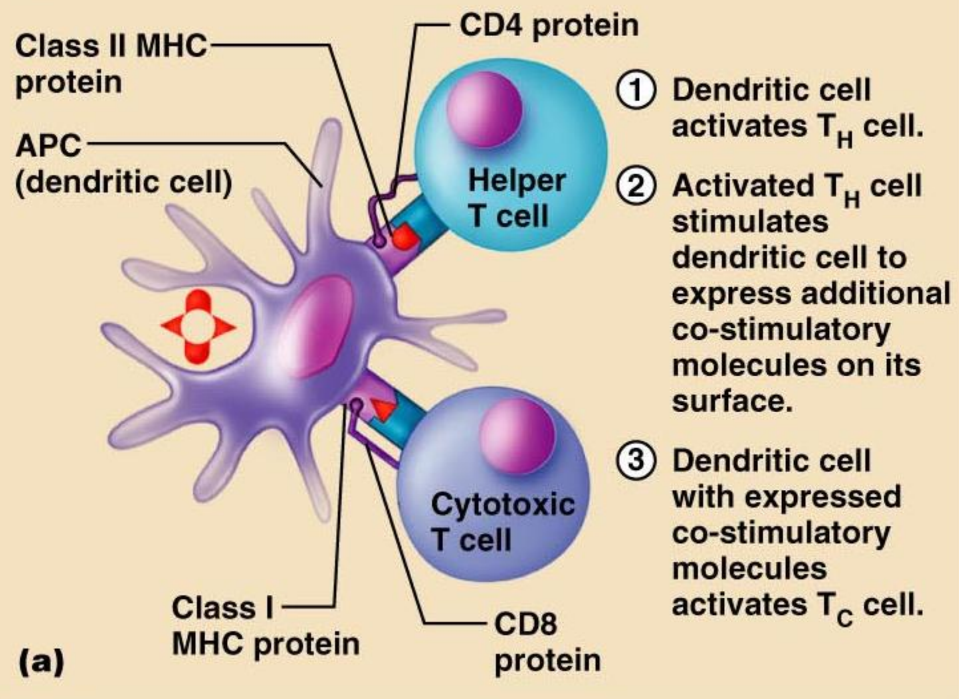
T Lymphocyte Activity

- Primary T cell response usually peaks within a week
- T cells then undergo apoptosis within a month
- Reduced activity parallels elimination of antigen
- This is a negative feedback control
- A few Memory T cells remain to respond to any future exposure to the same antigen

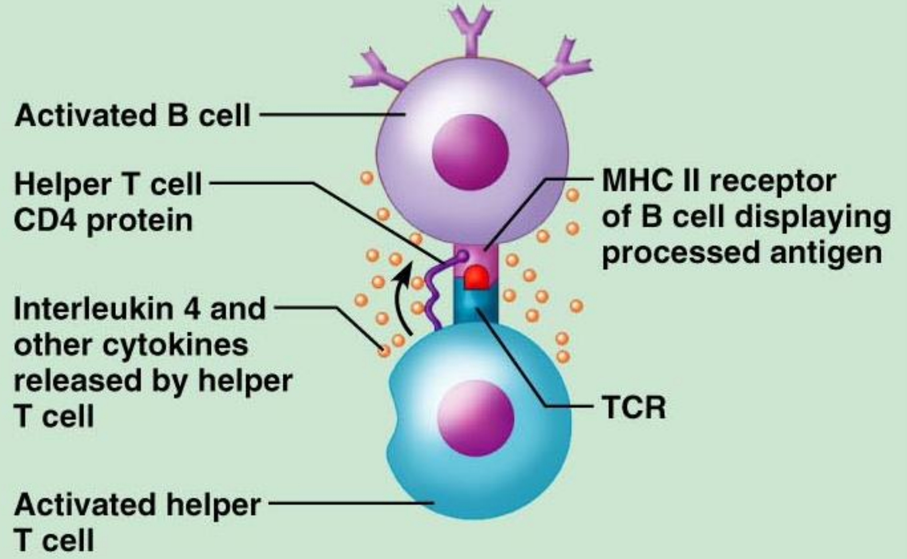
Helper T_H Lymphocytes

- Regulatory cells that play a central management role in the immune response
- Once primed by APC antigen presentation, T_H cells:
  - Stimulate proliferation of other T cell classes
  - Stimulate B cells that have already become bound to antigen
- There is ***NO*** coordinated immune response without T_H cell function

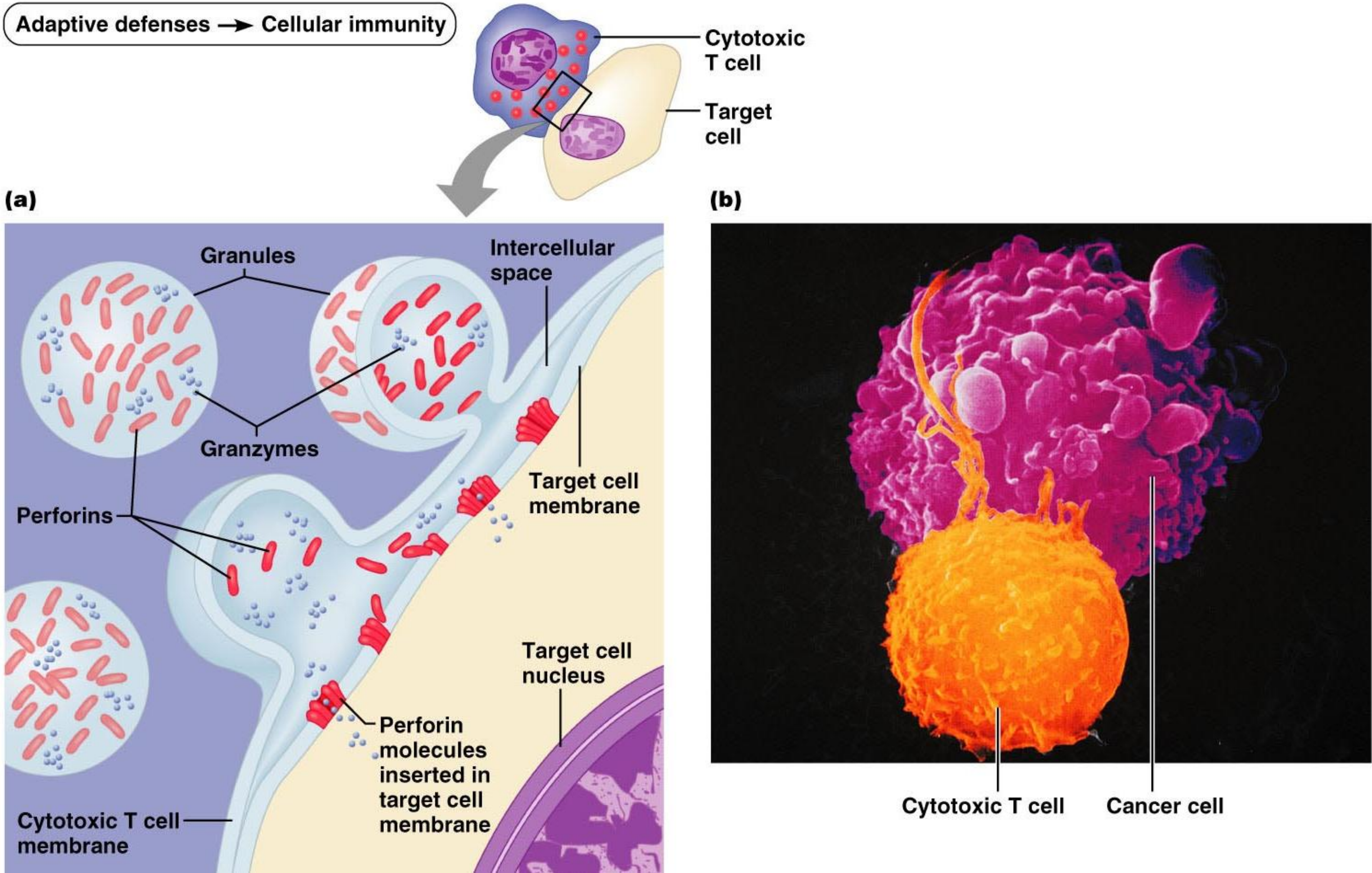
T_H cell help in cell-mediated immunity


Class II MHC protein
CD4 protein
APC (dendritic cell)
Helper T cell
① Dendritic cell activates T_H cell.
② Activated T_H cell stimulates dendritic cell to express additional co-stimulatory molecules on its surface.
③ Dendritic cell with expressed co-stimulatory molecules activates T_C cell.
Cytotoxic T cell
Class I MHC protein
CD8 protein
(a)

T_H cell help in humoral immunity


Activated B cell
Helper T cell CD4 protein
MHC II receptor of B cell displaying processed antigen
Interleukin 4 and other cytokines released by helper T cell
TCR
Activated helper T cell

Cytotoxic T_c Lymphocyte Actions



Suppressor T_S Lymphocytes

- T_S cells – immune regulatory cells which release cytokines that suppress the activity of both T cells and B cells
- Generated when other specific T cell clones are generated
- Negative feedback control to bring the body back to normal after the “battle” has been won

Antibody-Mediated Immunity

- Antigen challenge – the first encounter between an antigen and a naive B lymphocyte

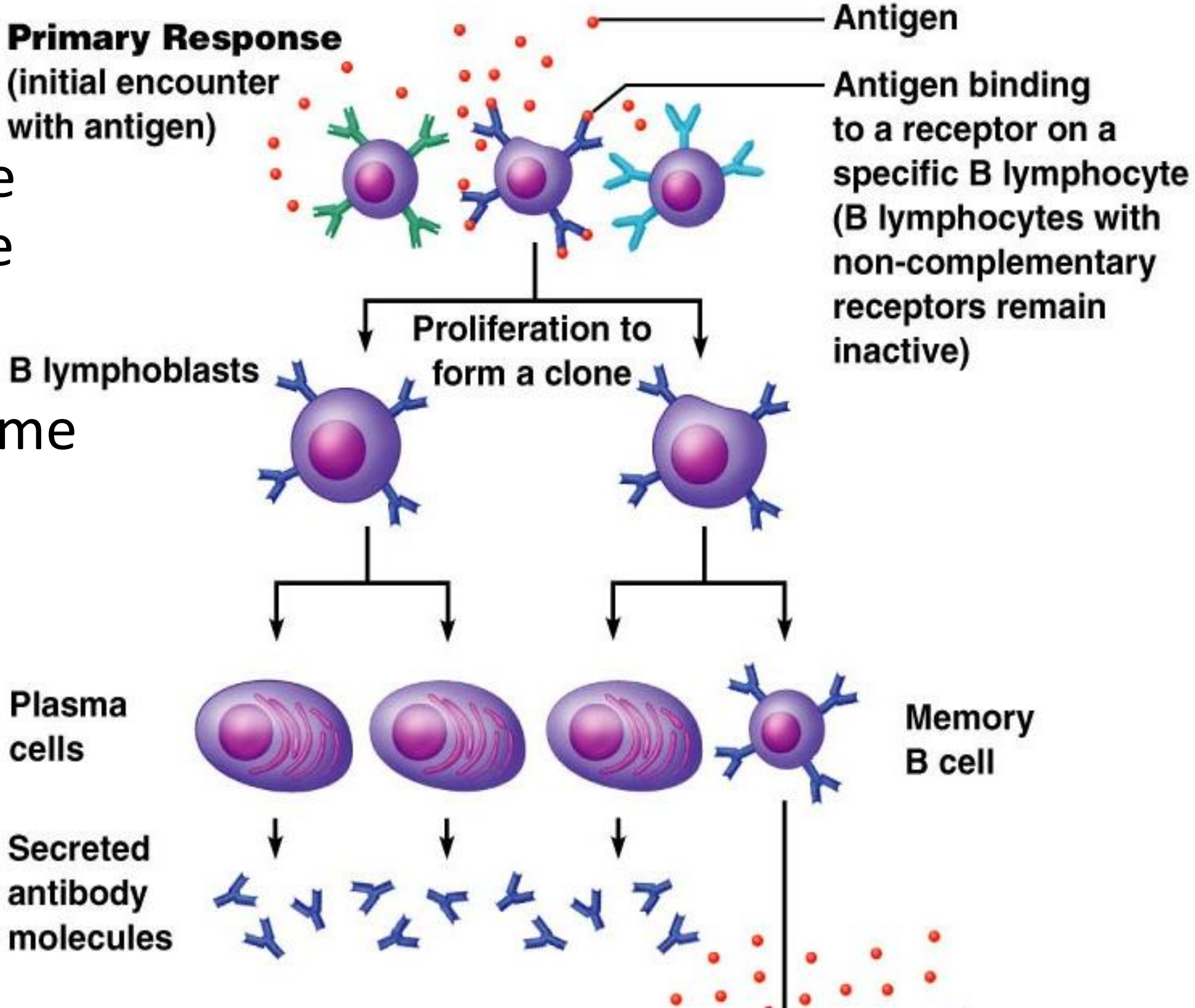
- Antigen presentation usually occurs in the spleen or a lymph node, but can occur in any lymphoid tissue
- Antigen presentation usually made by a macrophage, but some B cells can react directly against certain bacterial antigens

- Binding of the antigen to the B cell’s specific Ag receptor activates the B cell

Primary Response

Activated B cells grow and divide, forming clones bearing the same antigen-specific receptors and secreting the same antigen-specific Ab

- Most clone cells become plasma cells that secrete specific antibodies
- Clones that do not become plasma cells become B memory cells that can respond to subsequent exposures to the same antigen

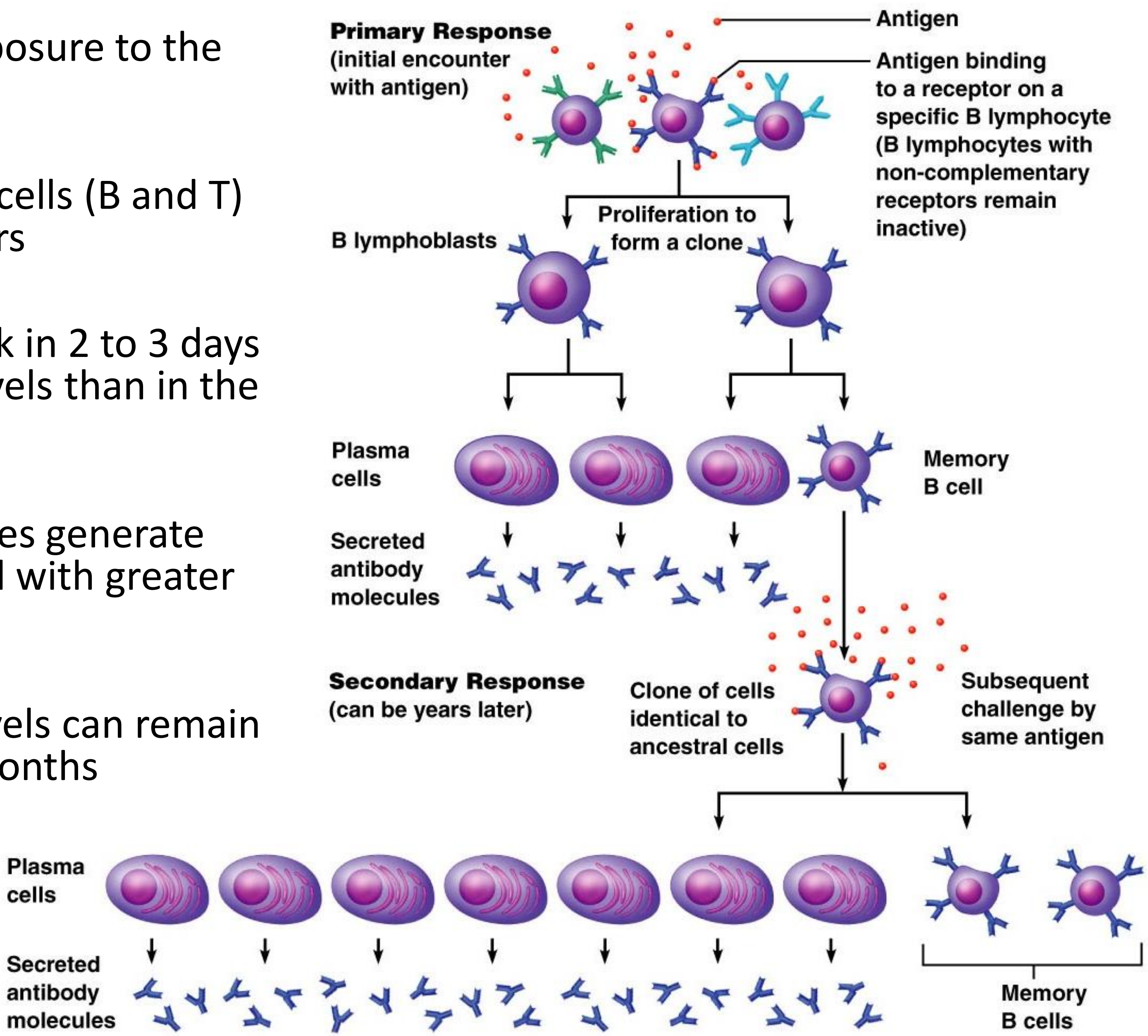

Primary Response
(initial encounter with antigen)
Antigen
Antigen binding to a receptor on a specific B lymphocyte (B lymphocytes with non-complementary receptors remain inactive)
Proliferation to form a clone
B lymphoblasts
Plasma cells
Memory B cell
Secreted antibody molecules

Primary Response

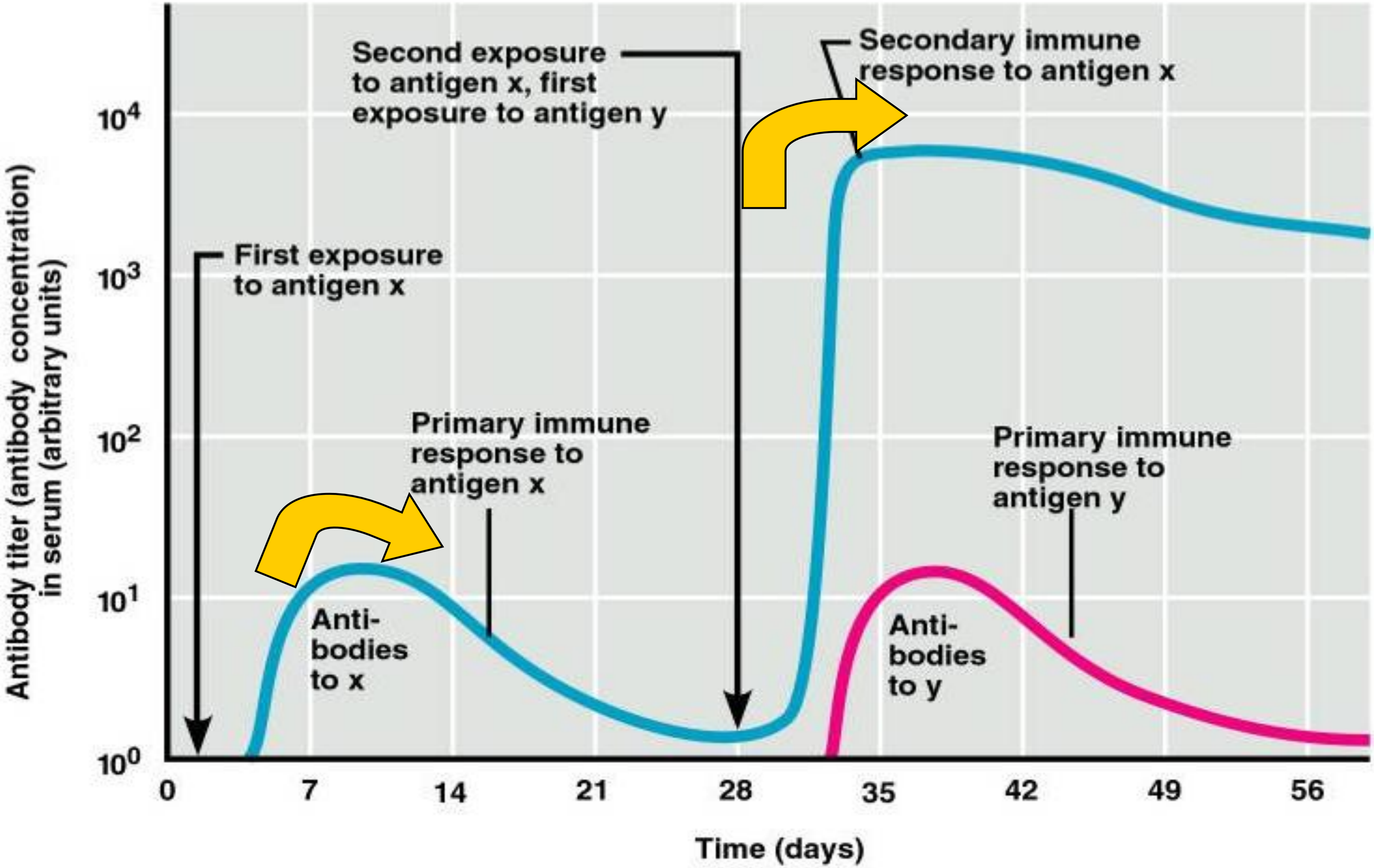
- Initial B cell differentiation, proliferation, and Ab synthesis requires time after the first Ag exposure
- Lag period: 3 to 6 days after antigen challenge
- Peak plasma levels of antibody are achieved in ~10 days
- Antibody molecules also reach the interstitial fluids, especially where inflammation exists
- Antibody levels then decline gradually if there is no additional Ag exposure

Secondary Response

- Any subsequent exposure to the same antigen
- Sensitized memory cells (B and T) respond within hours
- Antibody levels peak in 2 to 3 days at higher plasma levels than in the primary response
- Activated B subclones generate antibodies that bind with greater affinity
- Plasma antibody levels can remain high for weeks to months

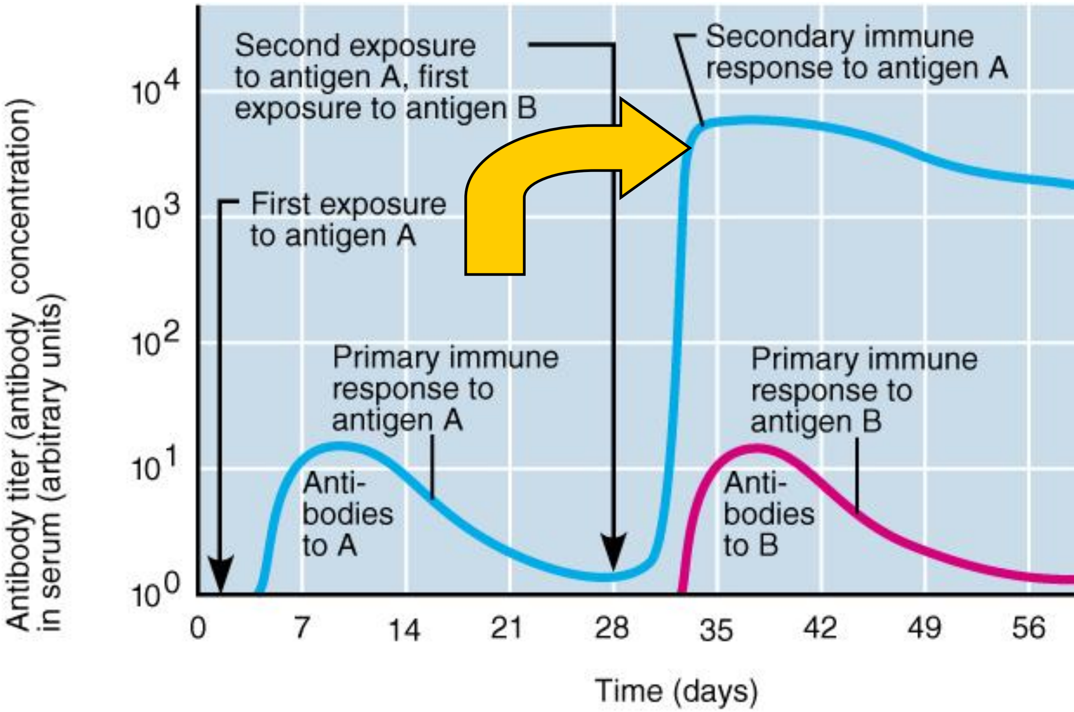

Primary Response
(initial encounter with antigen)
Antigen
Antigen binding to a receptor on a specific B lymphocyte (B lymphocytes with non-complementary receptors remain inactive)
B lymphoblasts
Proliferation to form a clone
Plasma cells
Memory B cell
Secreted antibody molecules
Secondary Response
(can be years later)
Clone of cells identical to ancestral cells
Subsequent challenge by same antigen
Plasma cells
Secreted antibody molecules
Memory B cells

Primary and Secondary Antibody Responses



Immunological Memory

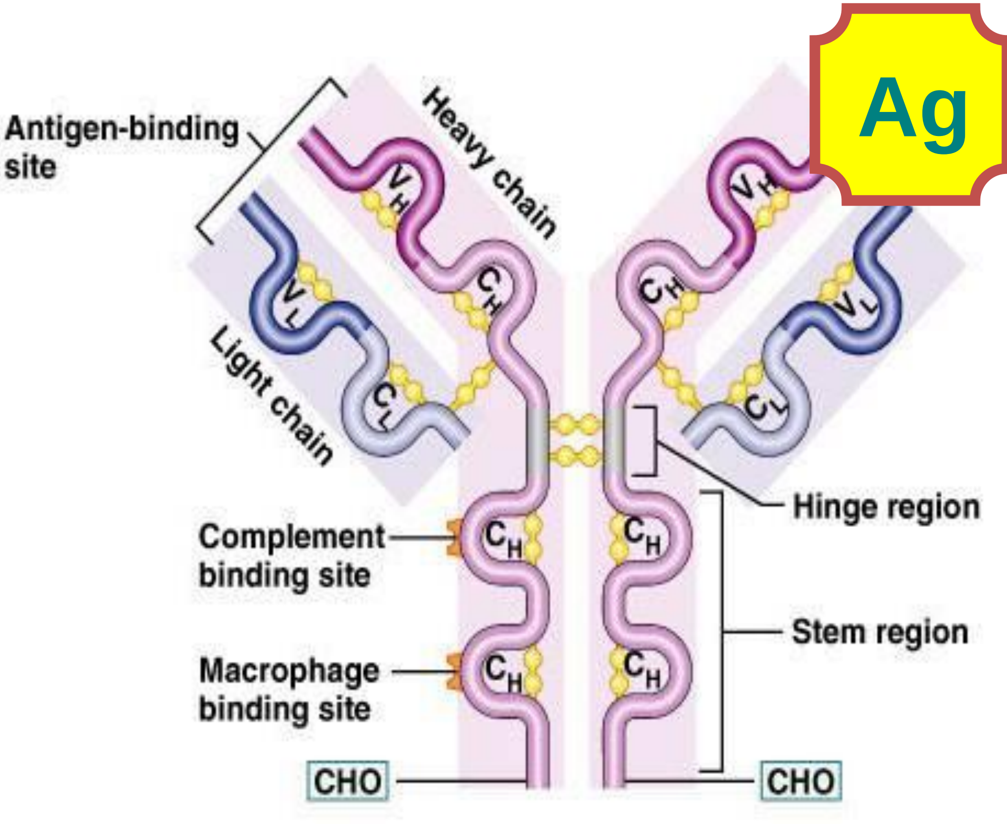
- Immunization is possible because memory B cells and memory T cells persist after the initial Ag exposure



- with any subsequent exposure, the immune system responds more quickly, forcefully
- secondary response - antibodies produced during subsequent exposures are produced in greater quantities and have a greater attraction for antigen

Basic Antibody Structure

- Four polypeptide chains linked together with disulfide bonds
- The four chains bound together form an **antibody monomer**
- Each chain has a variable (V) region at one end and a constant (C) region at the other
- *Variable regions* of the heavy and light chains combine to form the **antigen-binding site**



(a) Antibody molecule

Key:

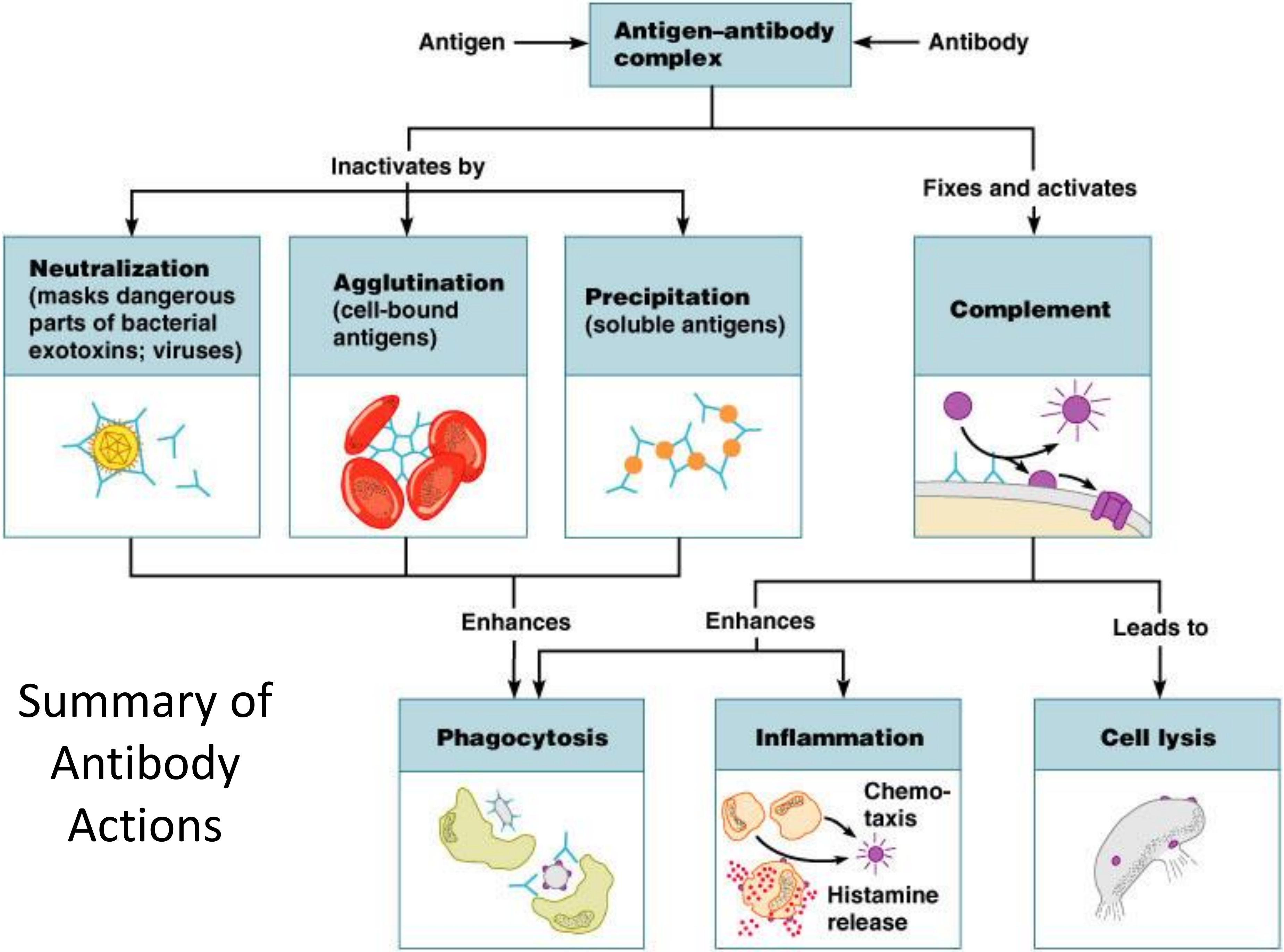
⚬⚬ = Disulfide bond

CHO = Carbohydrate side chain

Classes of Antibodies

- **IgD**: monomer attached to the surface of B cells, important in B cell activation
- **IgM**: pentamer released by plasma cells during the primary immune response
- **IgG**: monomer that is the most abundant and diverse antibody in primary and secondary responses; crosses the placenta and confers passive immunity
- **IgA**: dimer that helps prevent attachment of pathogens to mucosal surfaces
- **IgE**: monomer that binds to mast cells and basophils, causing histamine release when activated

Summary of Antibody Actions



Antigen → **Antigen–antibody complex** ← Antibody

Inactivates by

Neutralization (masks dangerous parts of bacterial exotoxins; viruses)

Agglutination (cell-bound antigens)

Precipitation (soluble antigens)

Fixes and activates

Complement

Enhances

Enhances

Leads to

Phagocytosis

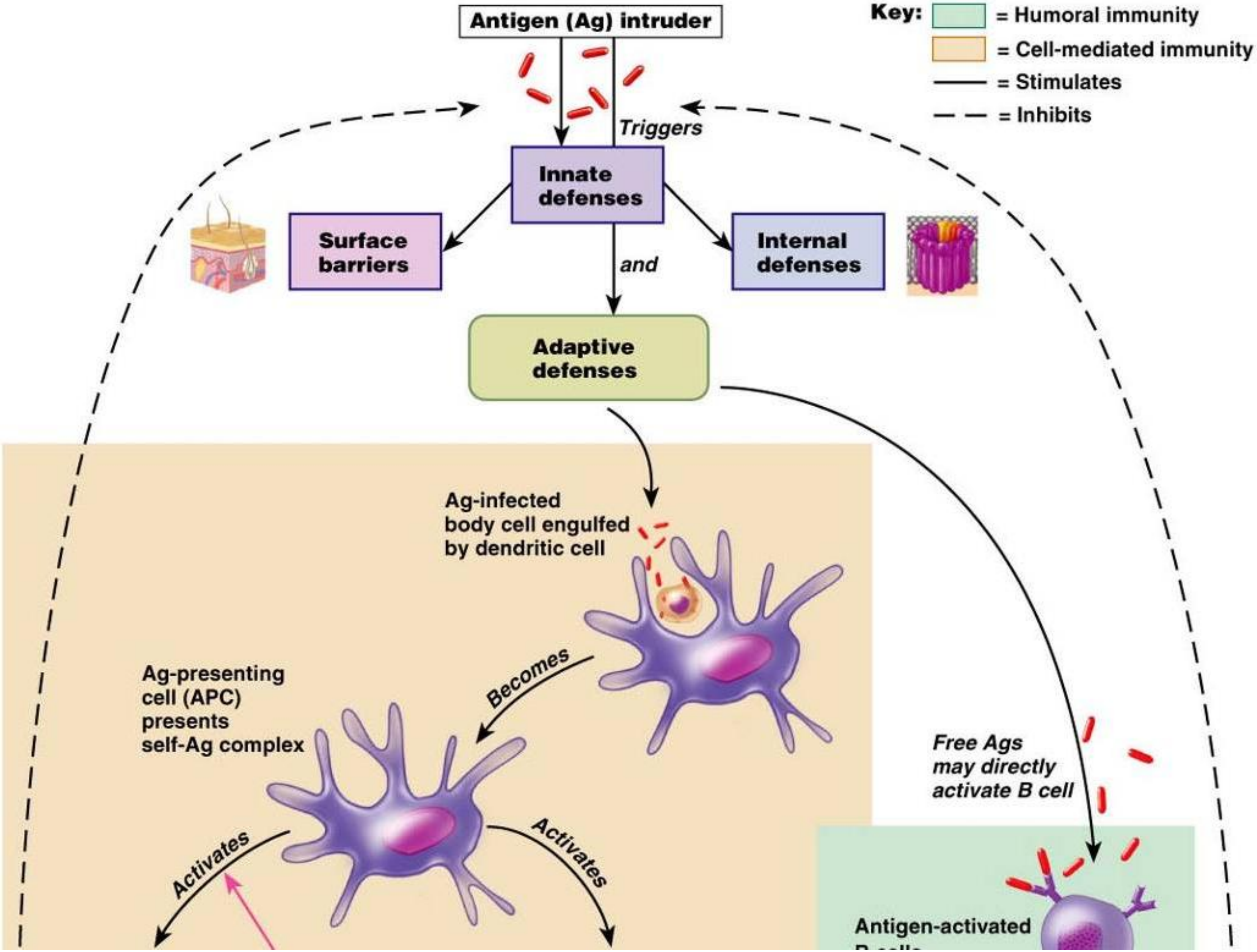
Inflammation

Cell lysis

Figure 21.13

Monoclonal Antibodies

- Monoclonal antibodies are purified tissue culture preparations of a specific antibody for a single antigenic determinant which are produced from descendents of a single B cell
- Commercially prepared monoclonal antibodies are used:
  - To provide passive immunity
  - In research applications
  - In clinical laboratory testing
  - In the treatment of certain cancers



Key:
🟩 = Humoral immunity
🟧 = Cell-mediated immunity
—— = Stimulates
– – = Inhibits

Antigen (Ag) intruder

Triggers

Innate defenses

Surface barriers

and

Internal defenses

Adaptive defenses

Ag-infected body cell engulfed by dendritic cell

Becomes

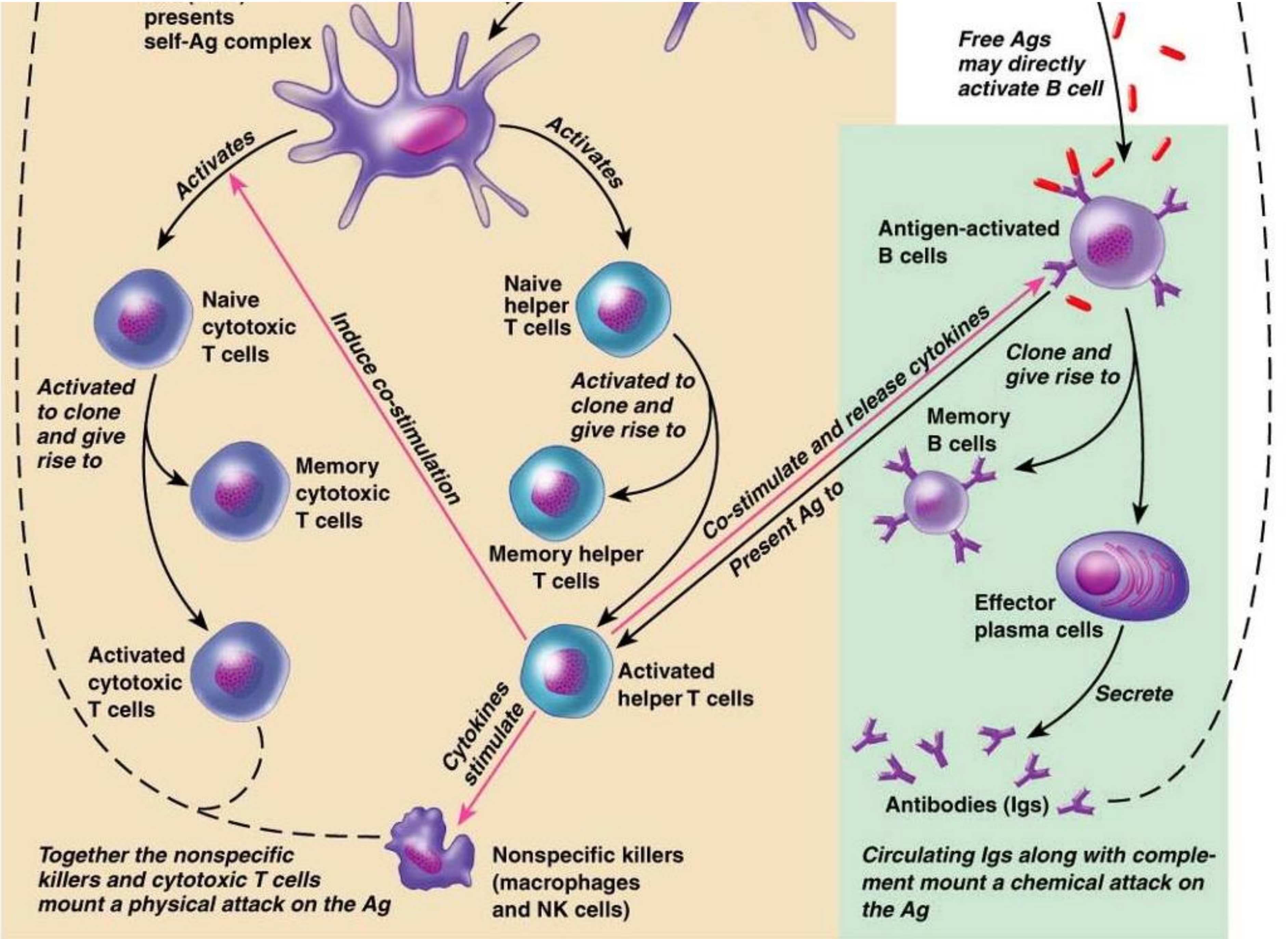
Ag-presenting cell (APC) presents self-Ag complex

Activates

Activates

Free Ags may directly activate B cell

Antigen-activated



presents
self-Ag complex

Free Ags may directly activate B cell

Activates

Activates

Naive cytotoxic T cells

Induce co-stimulation

Naive helper T cells

Antigen-activated B cells

Activated to clone and give rise to

Memory cytotoxic T cells

Activated to clone and give rise to

Memory helper T cells

Co-stimulate and release cytokines

Present Ag to

Clone and give rise to

Memory B cells

Effector plasma cells

Activated cytotoxic T cells

Activated helper T cells

Cytokines stimulate

Secrete

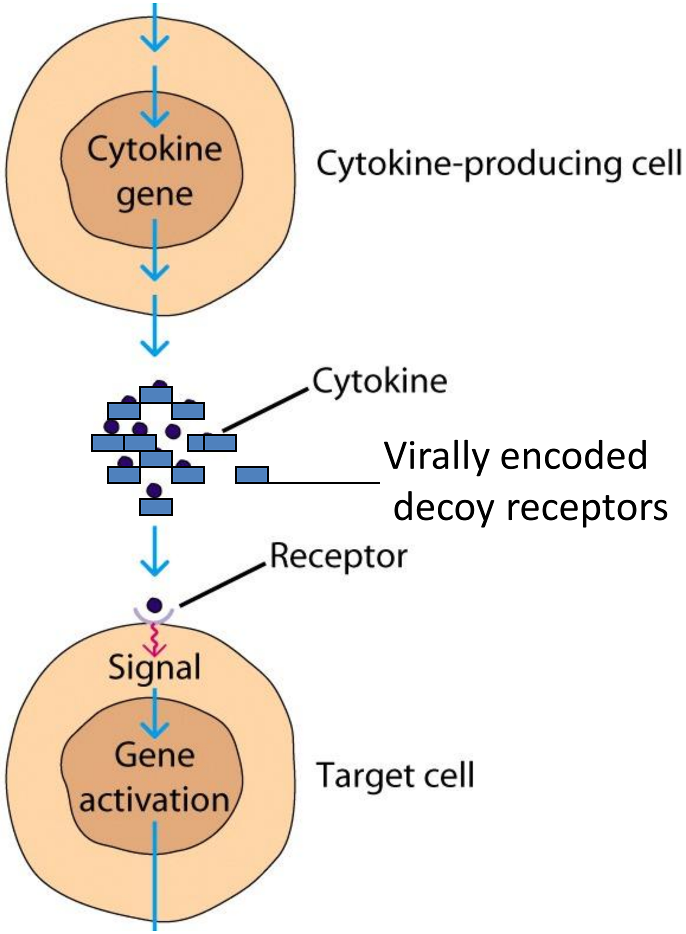
Antibodies (Igs)

Nonspecific killers (macrophages and NK cells)

Together the nonspecific killers and cytotoxic T cells mount a physical attack on the Ag

Circulating Igs along with complement mount a chemical attack on the Ag

Pathogens rapidly evolve to avoid the host immune response



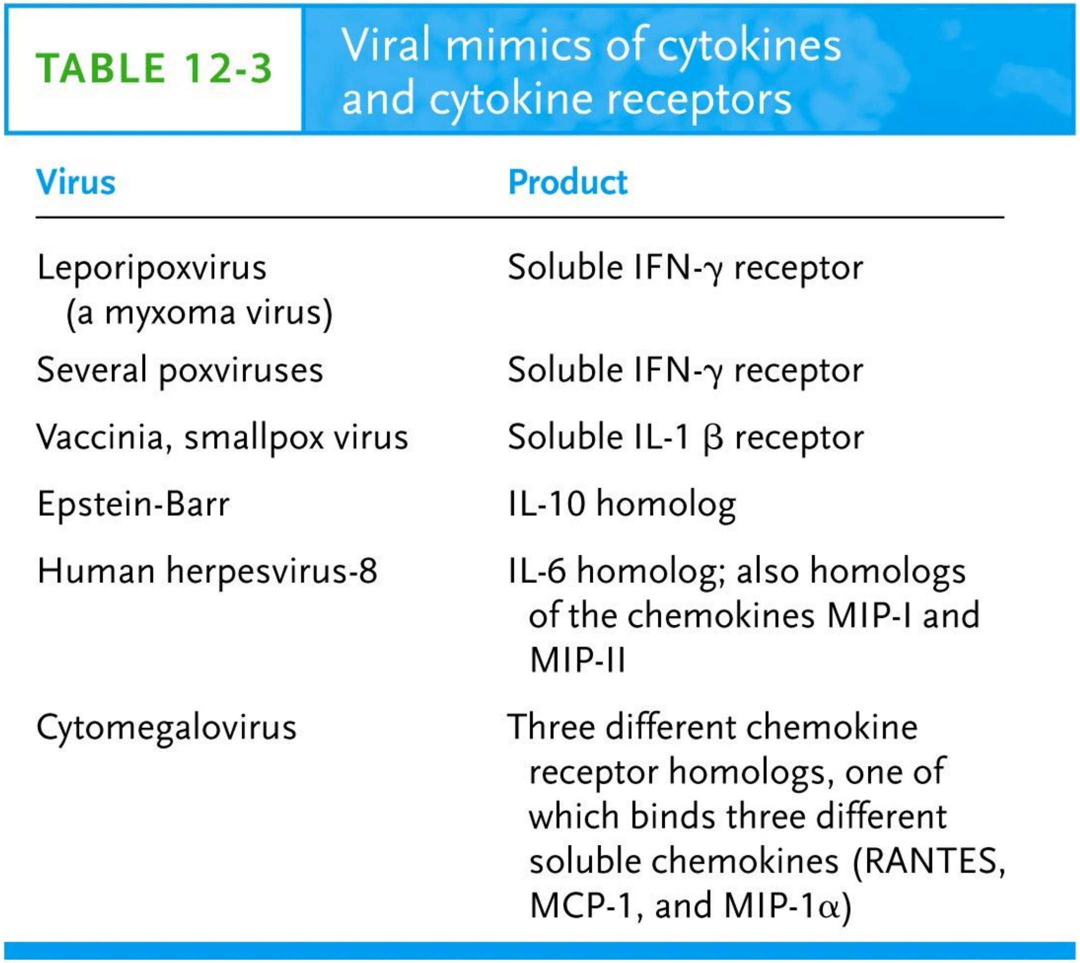
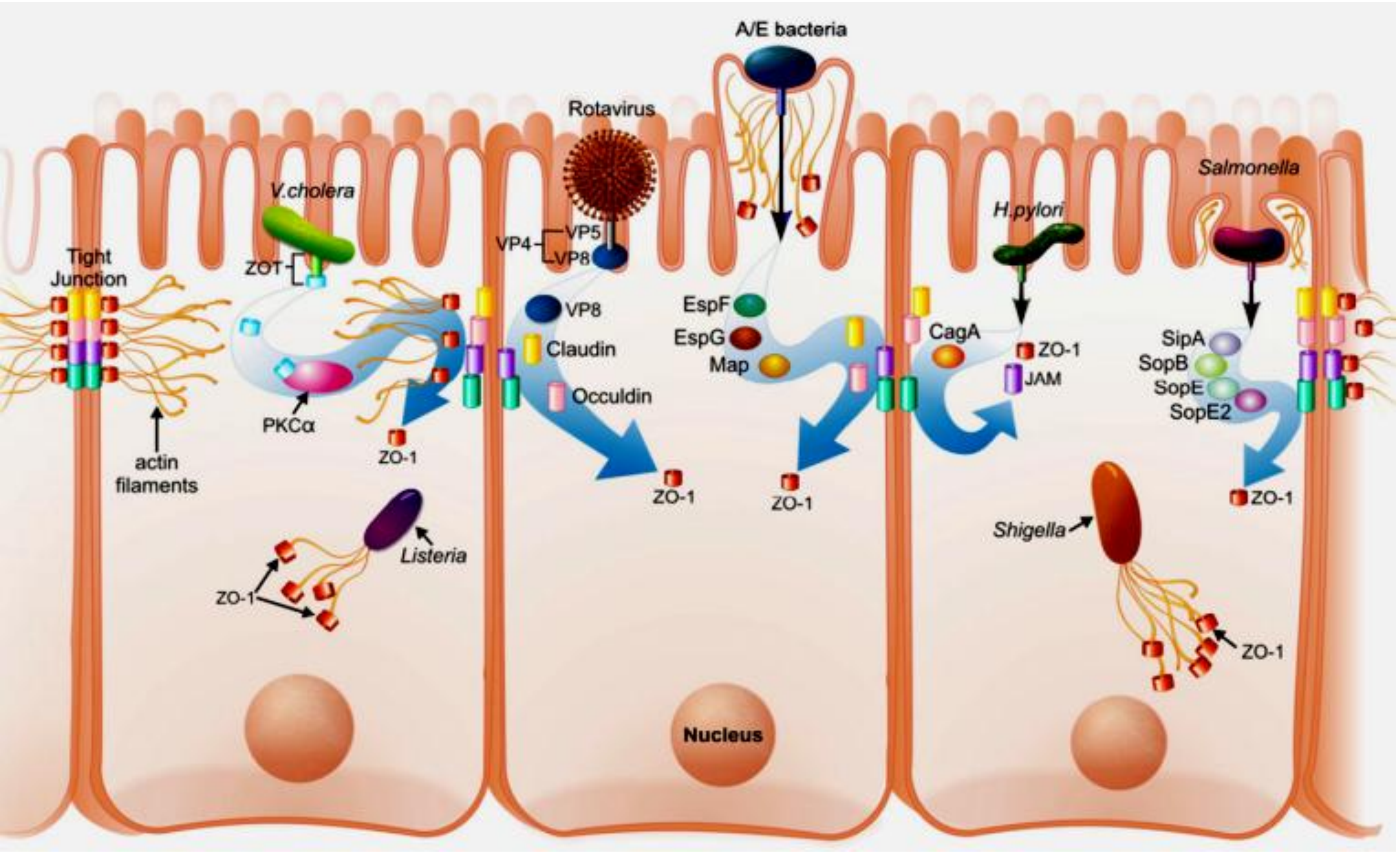
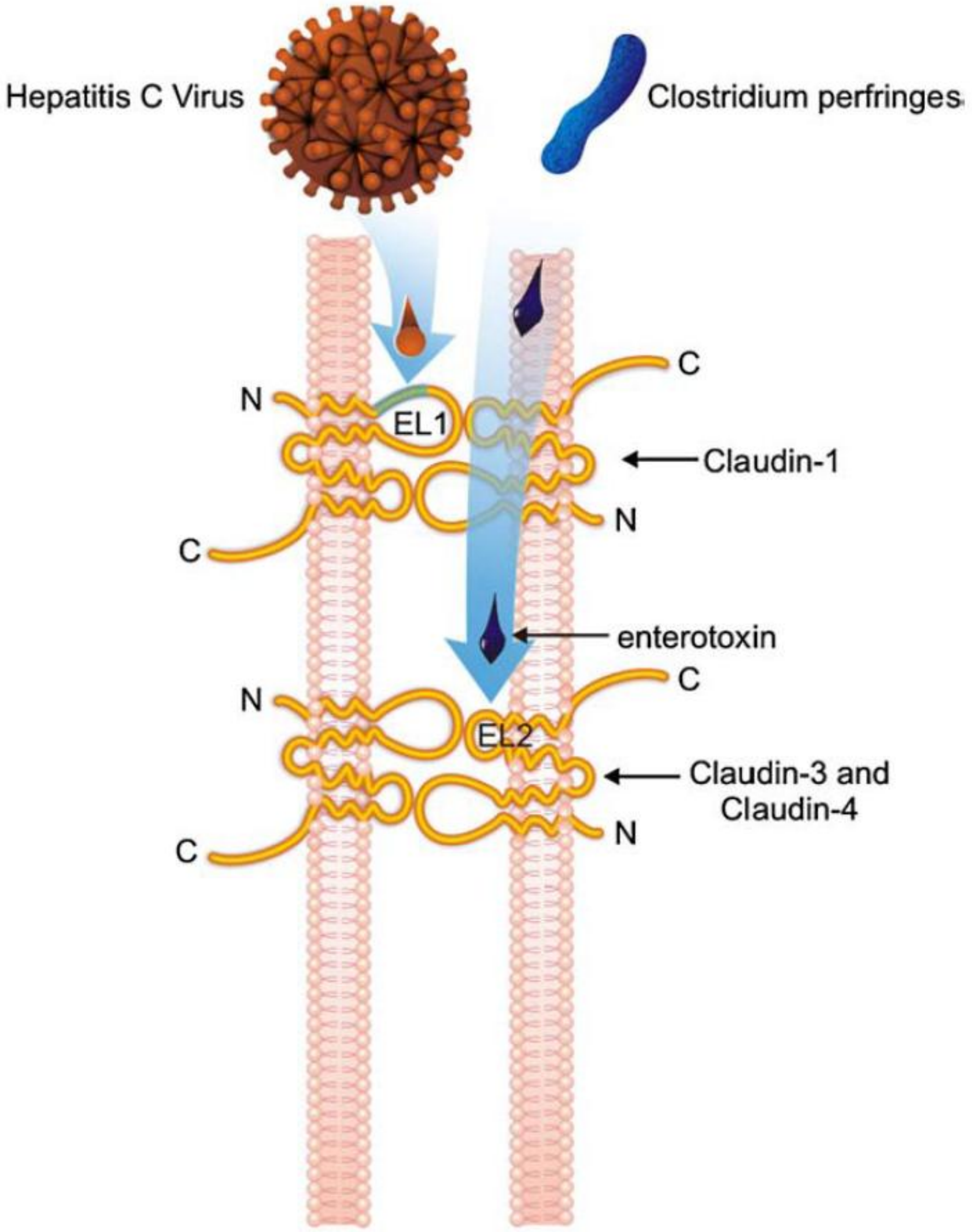


TABLE 12-3 Viral mimics of cytokines and cytokine receptors

Virus	Product
Leporipoxvirus (a myxoma virus)	Soluble IFN-γ receptor
Several poxviruses	Soluble IFN-γ receptor
Vaccinia, smallpox virus	Soluble IL-1 β receptor
Epstein-Barr	IL-10 homolog
Human herpesvirus-8	IL-6 homolog; also homologs of the chemokines MIP-I and MIP-II
Cytomegalovirus	Three different chemokine receptor homologs, one of which binds three different soluble chemokines (RANTES, MCP-1, and MIP-1α)

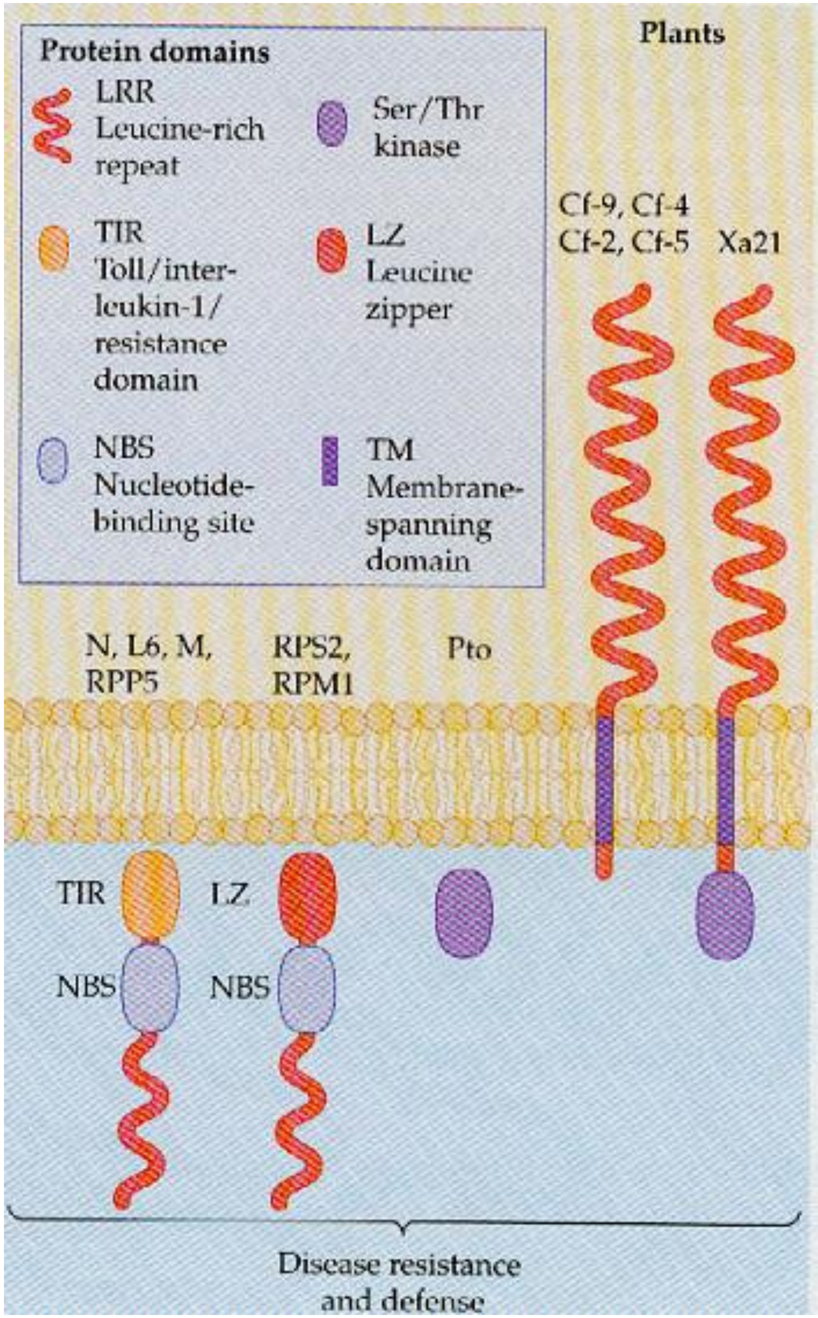

A/E bacteria
Rotavirus
V.cholera
Salmonella
H.pylori
Tight Junction
ZOT
VP4
VP5
VP8
VP8
Claudin
Occuldin
EspF
EspG
Map
CagA
ZO-1
JAM
SipA
SopB
SopE
SopE2
PKCα
actin filaments
ZO-1
ZO-1
ZO-1
ZO-1
Listeria
ZO-1
Shigella
ZO-1
Nucleus


Hepatitis C Virus
Clostridium perfringes
C
N
EL1
Claudin-1
N
C
enterotoxin
C
N
EL2
Claudin-3 and
Claudin-4
N
C

Plant immunity

Plant Resistance (R) Genes

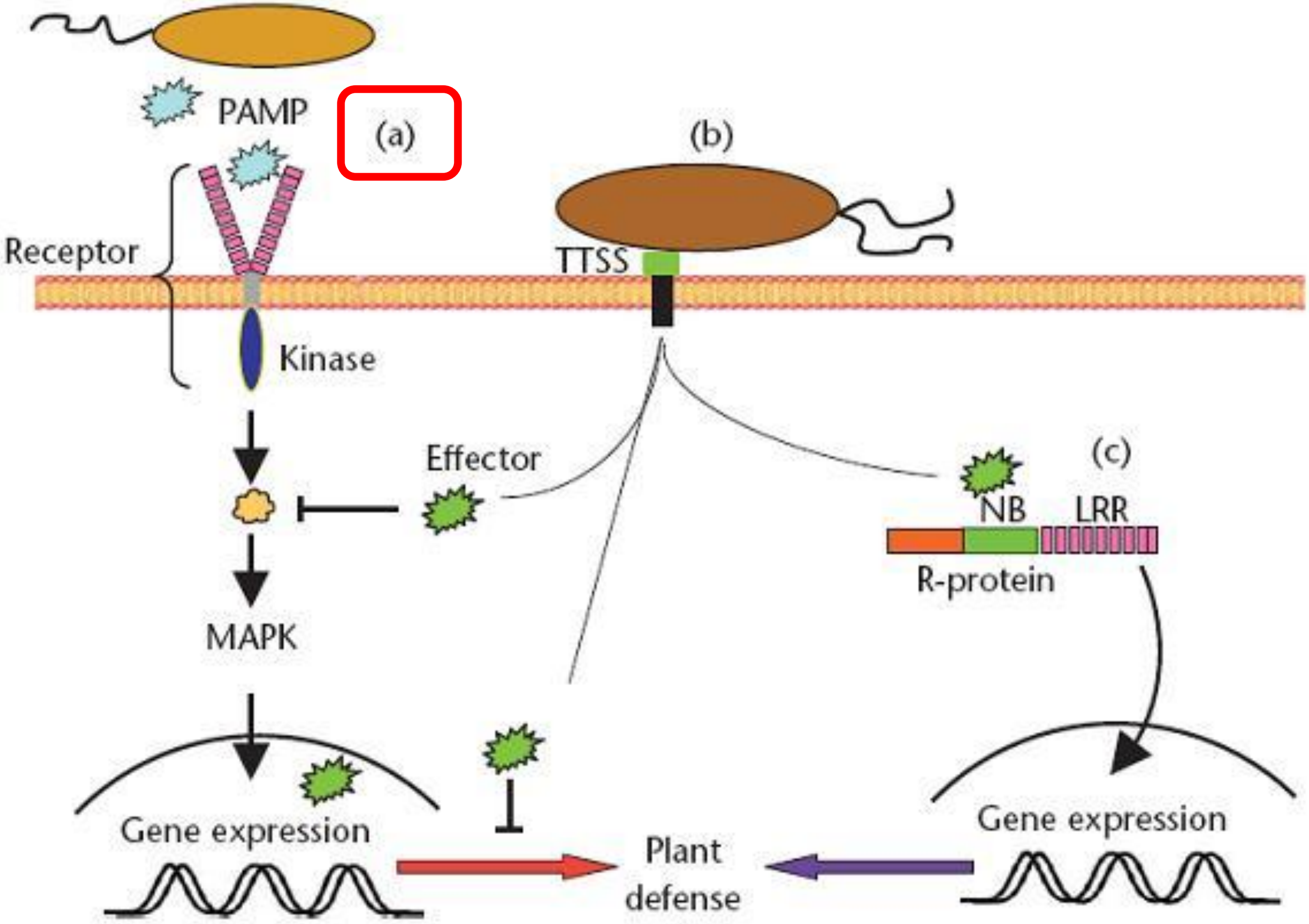
- Dominant
- Many ID so far
- 5 classes recognized
  - NBS: Nucleotide binding site
  - Leucine-zipper and leucine-rich repeat (LRR)
  - Toll/IL-1R (TIR)
  - Protein kinase (PK), receptor-like kinase (RLKs)



Gene on gene off action!

- Evolution of the plant–bacterial pathogen interaction.

(a) Plants have evolved receptors that could recognize P-AMPs and triggers basal defense.

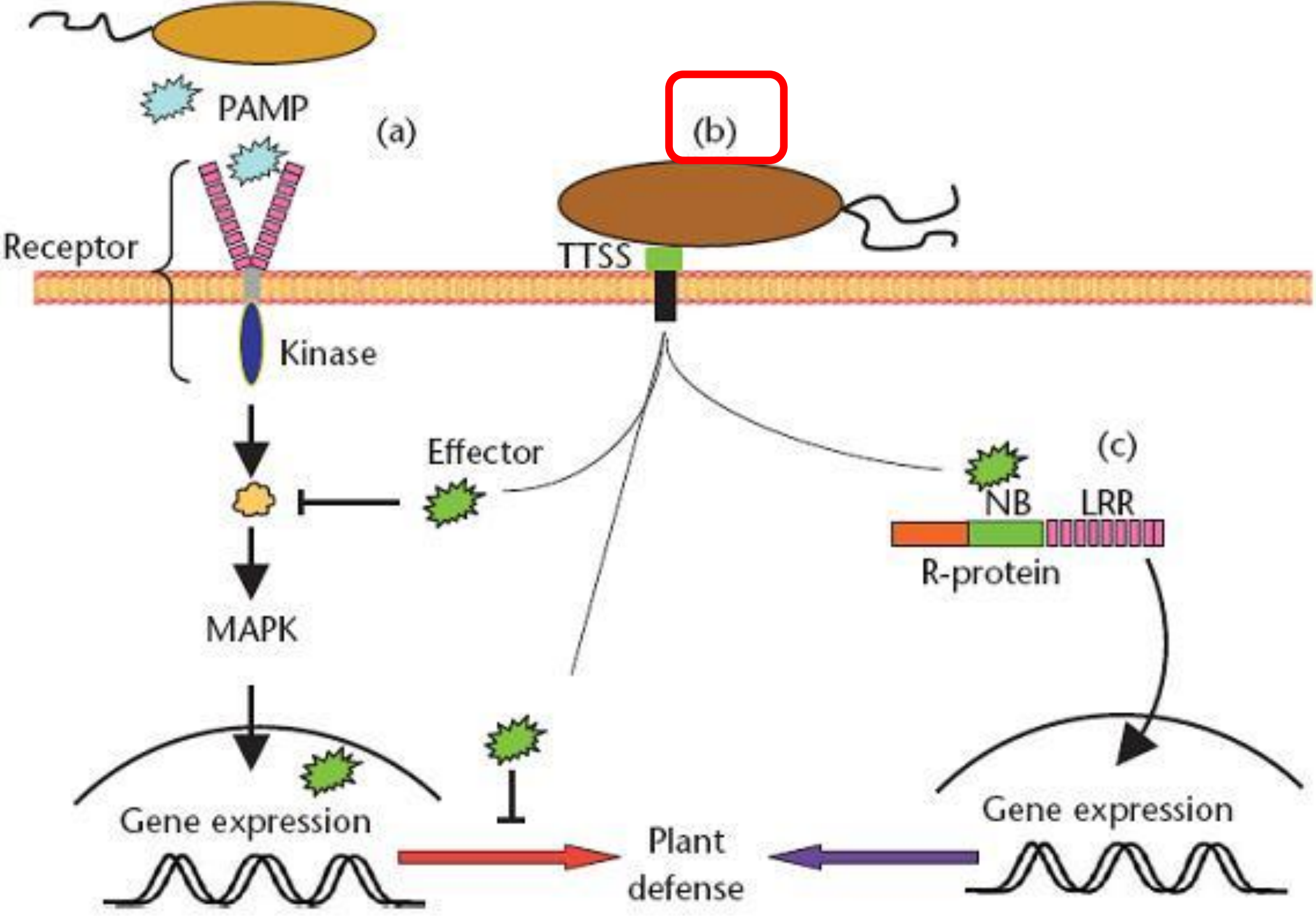


Gene on gene off action!

(b)

Bacterium injects effector protein through type III secretion system (TTSS)

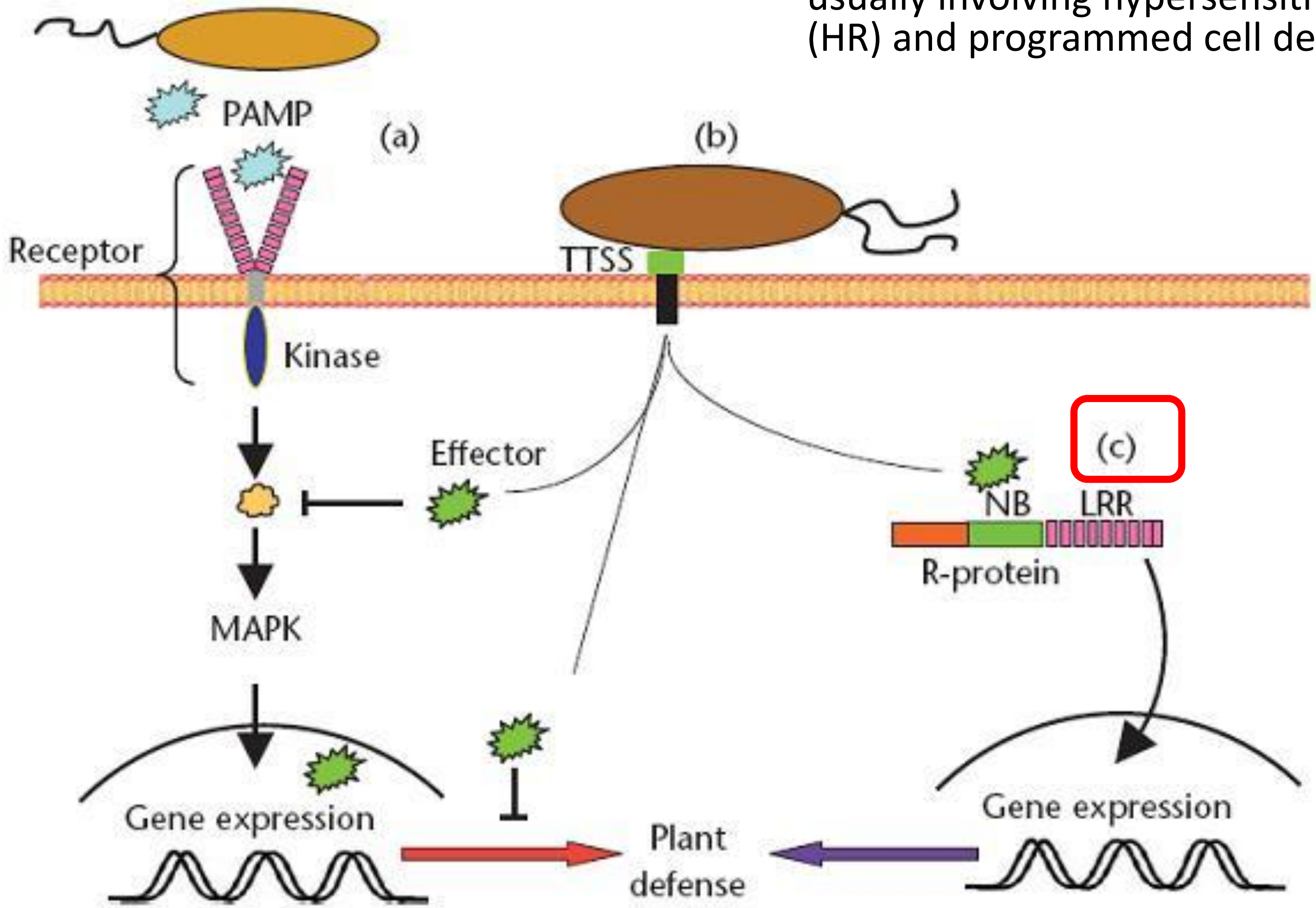
TTSS will interfere with defense signaling or response.



Gene on gene off action!

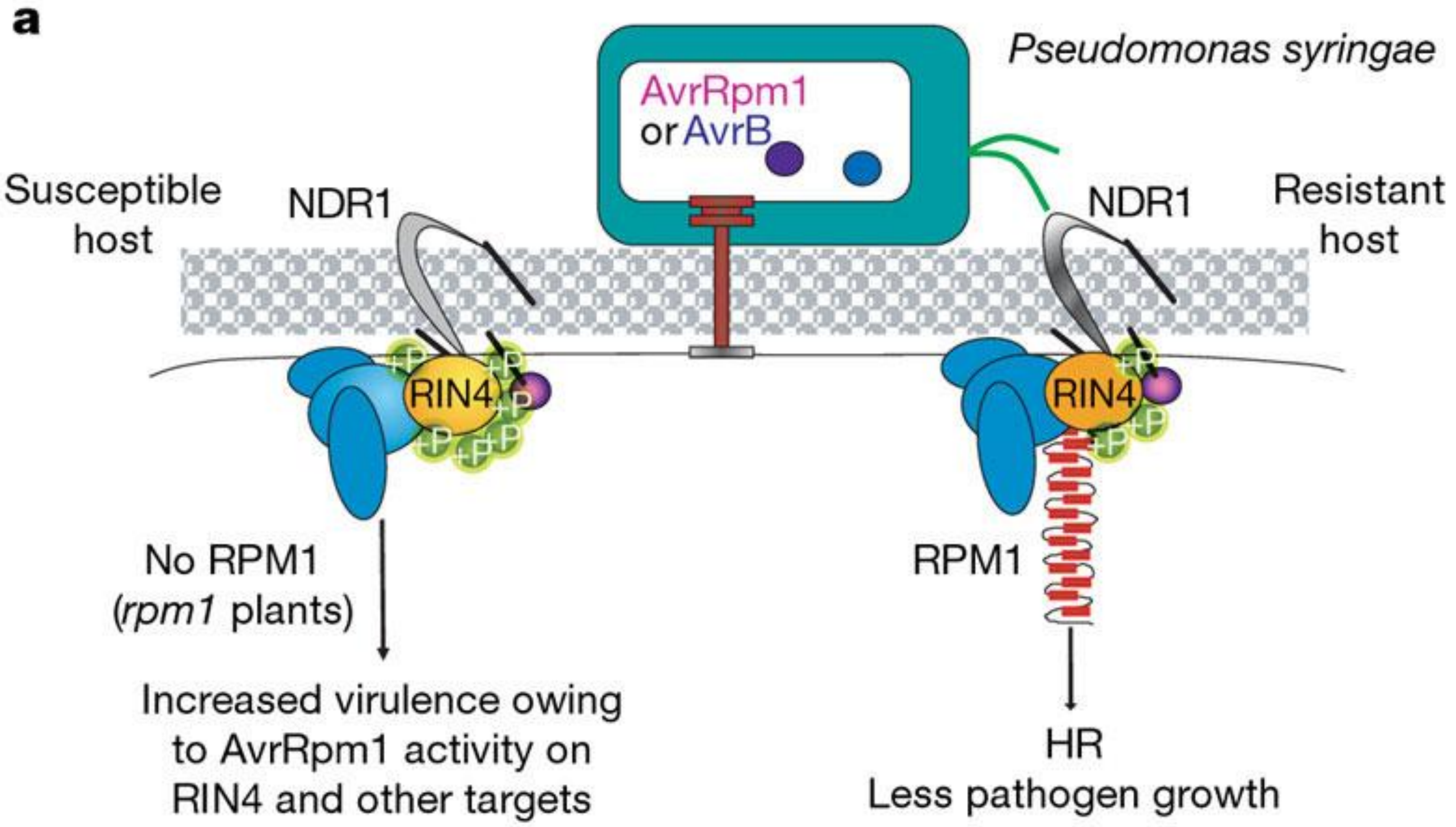
(c) Plant responds to infection by generation of immune receptors encoding for nucleotide-binding (NB), MAP kinase, leucine-rich-repeat (LRR)

R-proteins that recognizes effector protein and triggers an acute defense response usually involving hypersensitive response (HR) and programmed cell death



Pathogen recognition

- Gene-for-gene hypothesis: Upon infection by a particular avirulent pathogen, a corresponding R gene recognizes the *avr* product and triggers the defense mechanism.
  - Why do pathogens still possess *avr* genes?
- Non-host resistance: Resistance of all members of a host species against all members of pathogen species

a
Pseudomonas syringae
AvrRpm1
or AvrB
Susceptible host
NDR1
NDR1
Resistant host
RIN4
RIN4
P
No RPM1
(rpm1 plants)
RPM1
Increased virulence owing to AvrRpm1 activity on RIN4 and other targets
HR
Less pathogen growth

Induced defenses - biochemical

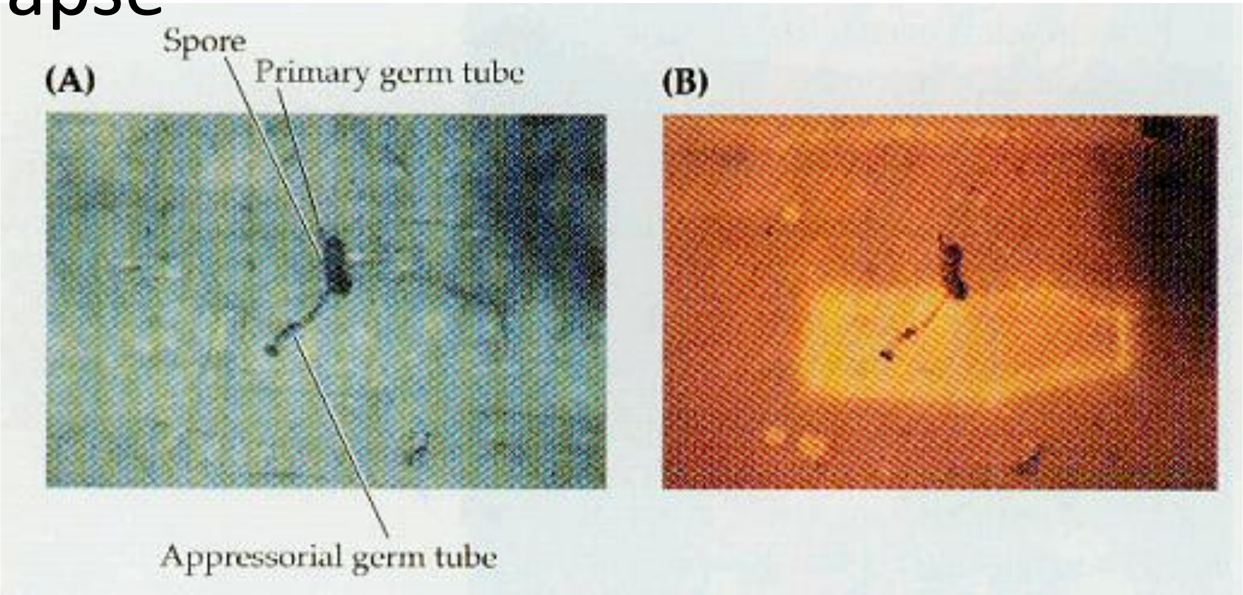
- Hypersensitive response (HR)
- Pathogenesis related (PR) proteins
- Phytoalexins
- Systemic Acquired Resistance (SAR)

Hypersensitive Response (HR)

- Burst of oxygen reactive species around infection site
- Synthesis of antimicrobial phytoalexins
- Accumulation of Salicylic Acid (SA)
- Directly kill and damage pathogens
- Strengthen cell walls, and triggers apoptosis
- Restrict pathogen from spreading
- Rapid and local

Hypersensitive response – programmed cell death

1. Recognition
2. Host membrane changes
3. Chemical attack
4. Cessation of cytoplasmic streaming
5. Membrane collapse



Wound healing – zone around wound/infection sacrificed for defense

1. Infused with phytoalexins and other phenoic compounds (tannins), gum, resin
2. Tissue dies
3. Cork barrier forms outside zone
4. Tissue differentiation
   a. Parenchyma – return to meristematic state
   b. Cork cambium
5. Wound isolated from living part of plant body

Immediate responses of invaded cells

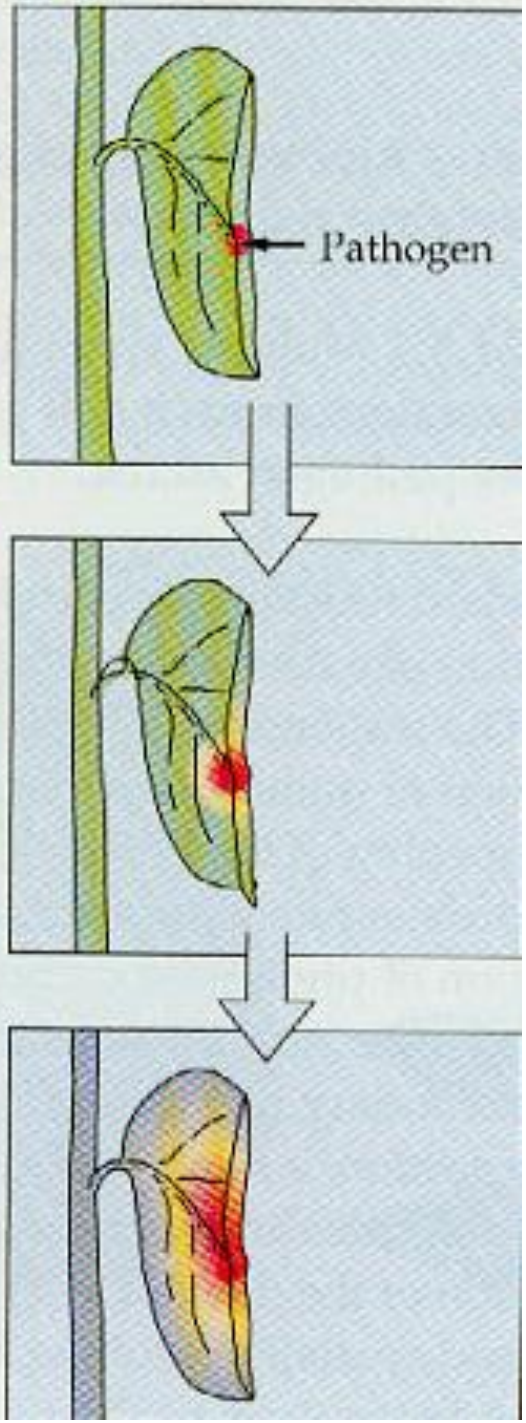
- Generation of reactive oxygen species
- Nitric oxide synthesis
- Opening of ion channels
- Protein phosphorylation/dephosphorylation
- Cytoskeletal rearrangements
- Hypersensitive cell death (HR)
- Gene induction

Local responses and gene activation

- Alterations in secondary metabolic pathways
- Cessation of cell cycle
- Synthesis of pathogenesis-related (PR) proteins
- Accumulation of benzoic and salicylic acid
- Production of ethylene and jasmonic acid
- Fortification of cell walls (lignin, PGIPs, HRGPs)

Systemic responses and gene activation

- (1→3)β-Glucanases
- Chitinases
- Peroxidases
- Synthesis of other PR proteins



Pathogen-Related (PR) Genes

- Antimicrobial properties
- Many identified
- Categorized according to activity
- Examples
  - PR-2 : beta-1,3-glucanase
  - PR-3 : chitinase
  - PR-12: defensin

What do the Avirulence genes (avr genes) code for?

- They are VERY diverse!
- Bacteria
  - Cytoplasmic enzymes involved in the synthesis of secreted elicitor
- Fungi
  - Secreted proteins
  - Fungal toxins

What do the Resistance genes (R genes) code for?

- They are ALSO diverse!
- Enzymes
  - Inactivate toxins
  - Signal initiation of the defense responses
- Membrane receptor proteins
- Proteins that interact with other proteins

Systemic Acquire Resistance (SAR)

- Secondary response
- Systemic
- Broad-range resistance
- Leads to Pathogenesis-Related (PR) gene expression
- Signals: Salicylic acid, Jasmonates, ethylene

Systemic Acquired Resistance (SAR)

- Generalized resistance AFTER exposure to pathogen
- Enhanced capacity to mobilize infection-induced, cellular defense responses
- Reduces severity of disease from all pathogen types
- First – localized
- Next – spreads systemically

PLANT-PATHOGEN INTERACTIONS

INCOMPATIBLE

Host R-gene
Pathogen Avr gene(s)

HR

Salicylic acid

SAR

Local lesions, necrosis, no spread

COMPATIBLE

Host does not recognize pathogen

?

infection

Systemic spread, symptoms